ESSTS

Thursday, 18 June 2026, 16:15-16:45

Pharmacotherapy for Tics: Past & Future

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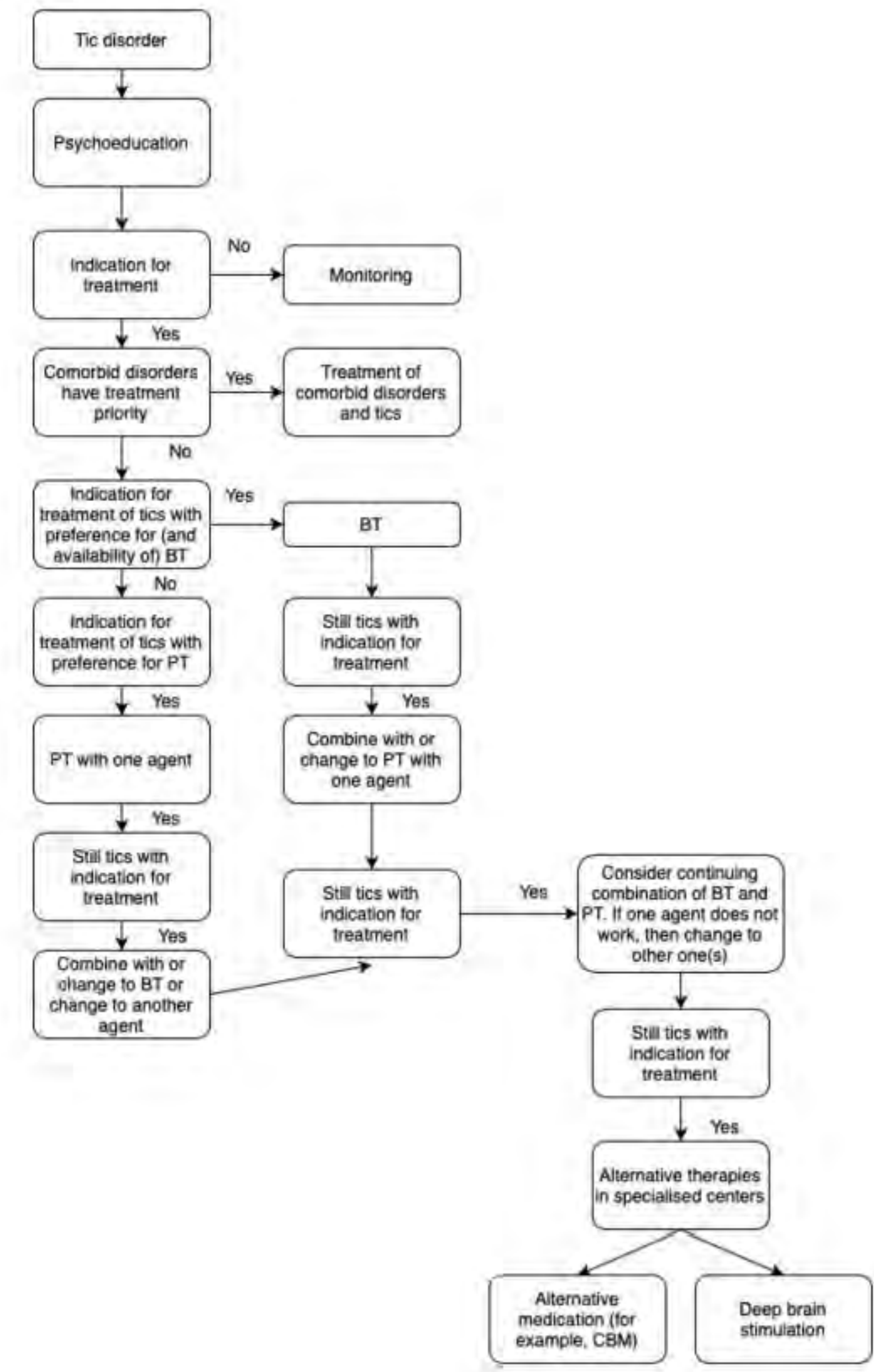

Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine

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]

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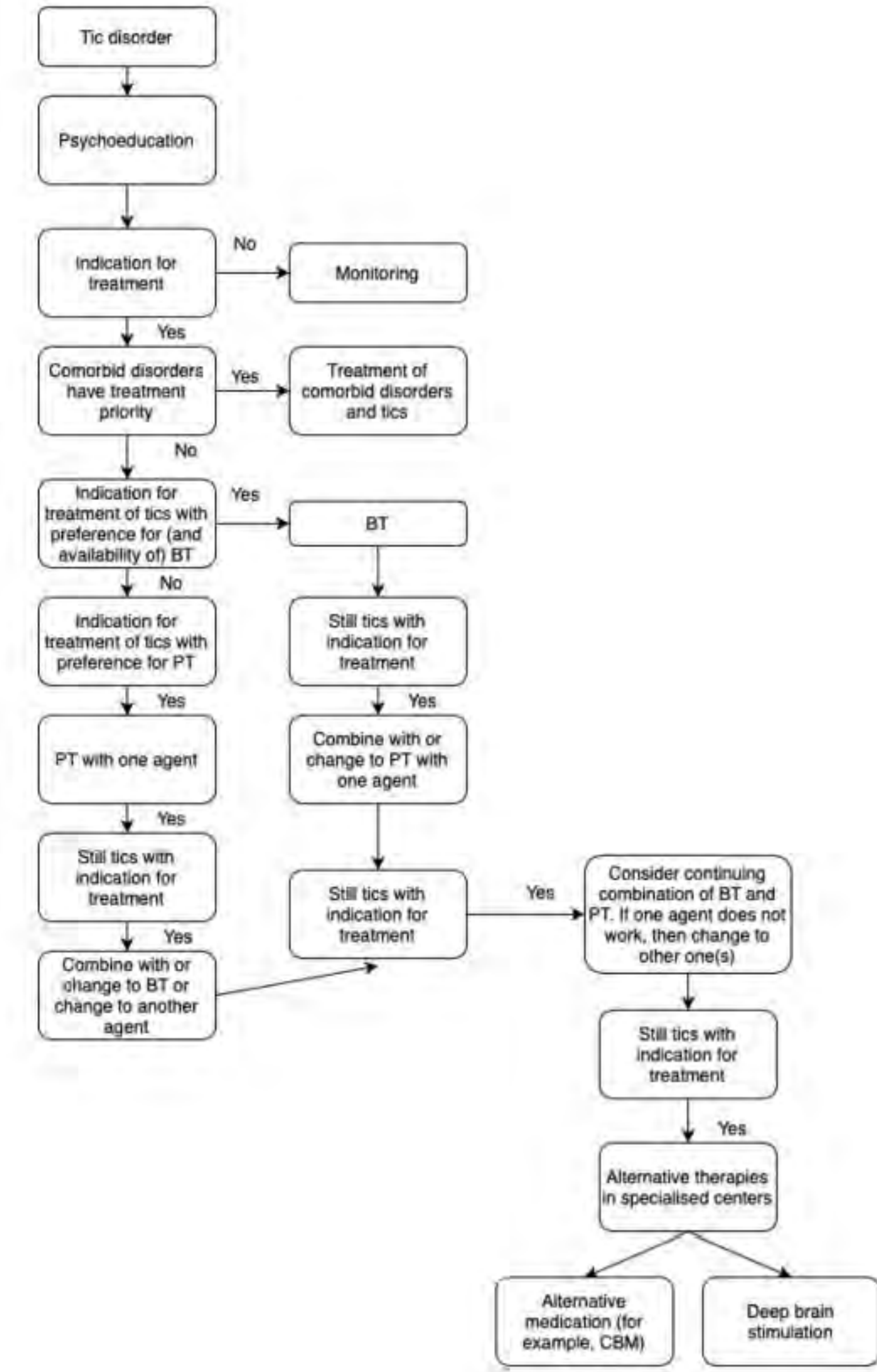
Part I:	Assessment
Part II:	Psychological interventions
Part III:	Pharmacological treatment
Part IV:	Deep brain stimulation

Summary statement
Patients' perspectives
Editorial



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Pharmacotherapy for Tics: Past & Future

PAST (1960s) → PRESENT / FUTURE (2026+)

Year	Drug	Brand	Status	Details
1967	HALOPERIDOL	Haldol	FIRST FDA APPROVED	Typical Neuroleptic (D_2 blocker); High risk of motor side effects (EPS)
1970s	SULPIRIDE	Dolmatil/Sulpor	PRIMARY EUR/ASIA USE	First-Gen Benzamide (D_2/D_3 blocker); Low sedation, widely used
1980s	TIAPRIDE	Tiapridal	EUR PEDIATRIC STANDARD	First-Gen Benzamide; Favorable safety, low metabolic/motor risks
1984	PIMOZIDE	Orap	FDA APPROVED	Typical Antipsychotic (D_2 blocker); Used for non-responders; Requires EKG monitoring
EARLY 2000s	TOPIRAMATE	Topamax	OFF-LABEL GLOBAL	Antiepileptic (GABA/Glutamate); Non-Dopaminergic; Avoids weight gain
2008	RISPERIDONE	Risperdal	GLOBAL OFF-LABEL/APPROVED	Atypical Antipsychotic (D_2/5-HT_{2A} blocker); Effective, higher metabolic risk
2014	ARIPIPRAZOLE	Abilify	FDA APPROVED (Modern Std.)	Dopamine Stabilizer (Partial D_2 Agonist); Well-tolerated, standard first-line US therapy
2026+	ECOPIPAM	INVESTIGATIONAL	FIRST-IN-CLASS D_1 ANTAGONIST	Targets D_1 receptor; Designed to eliminate D_2 side effects; In final trials

Created by AI

Licensed for Treatment of Tics/Tourette Syndrome

- US:
  - haloperidol
  - pimozide
  - aripiprazole

- Europe
  - haloperidol

ESSTS Survey: clinical practice: 2011 vs. 2019

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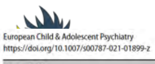
■ 2019 ■ 2011

aripiprazole
clonidine
tiapride
haloperidol
guanfacine
risperidone
tetrahydrocannabinol
atomoxetine
quetiapine
pimozide
topiramate
botulinum toxine
amisulpiride
tetrabenazine
sertraline
sulpiride
ziprasidone



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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]

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aripiprazole
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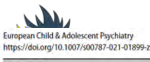
sertraline
sulpiride
ziprasidone



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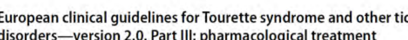

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Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: a systematic review and network meta-analysis

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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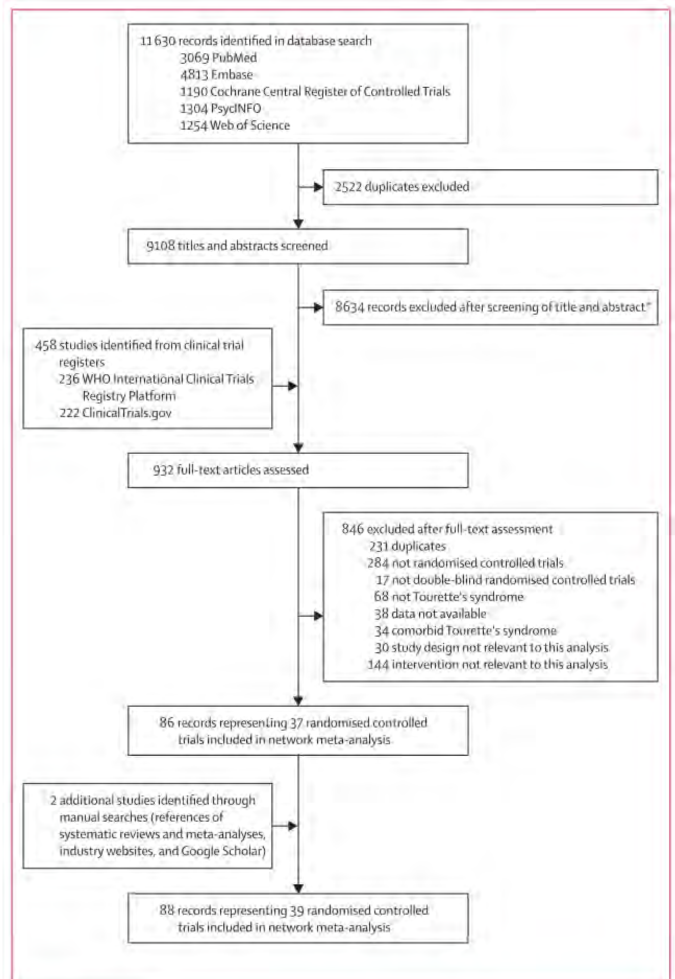
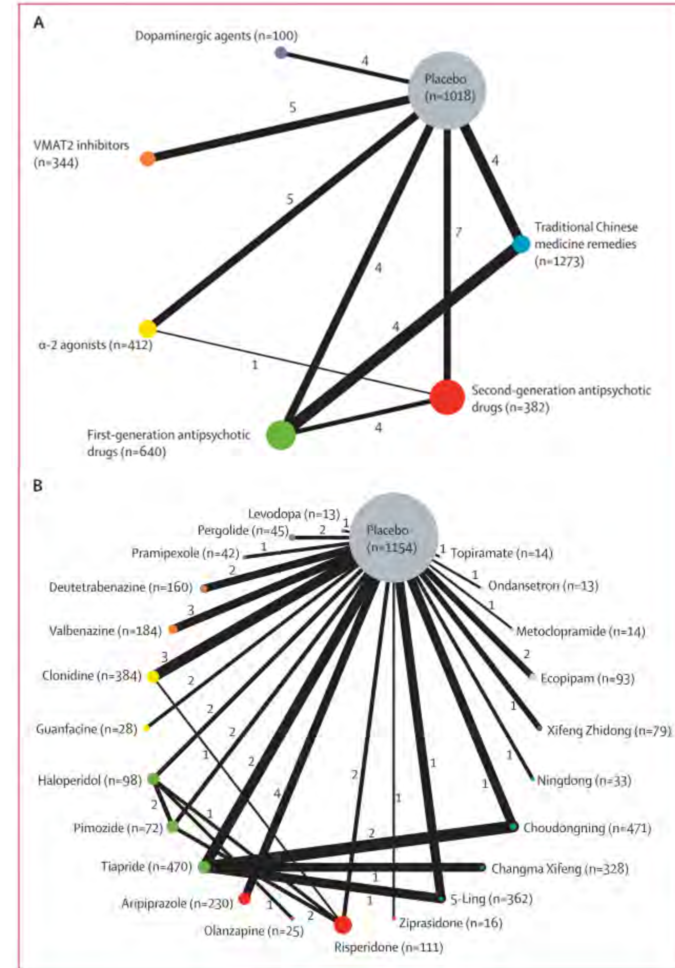


Figure 1: Study selection
*Main reasons for exclusion during screening of title and abstract were as follows: the studies did not focus on tic disorders, were not clinical trials, or did not assess pharmacological interventions.



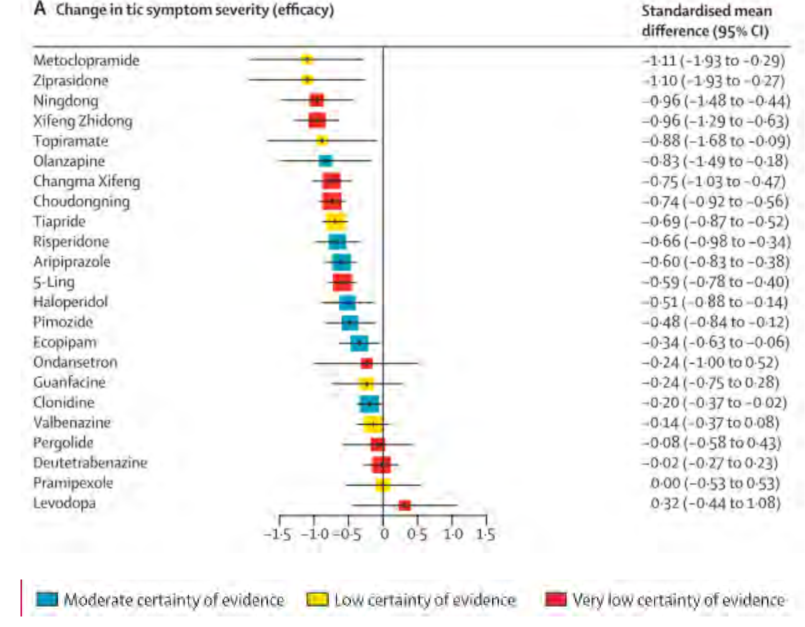
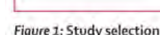


Figure 2: **Network plots for efficacy for medication categories (A) and medications individually (B)**
The nodes are coloured according to their medication category, and their size is proportional to the number of groups that included that treatment. The number of studies for each comparison is illustrated 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.



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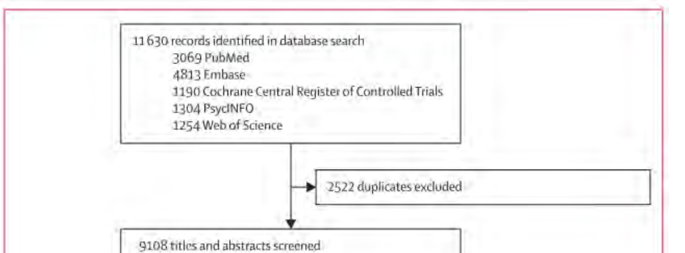
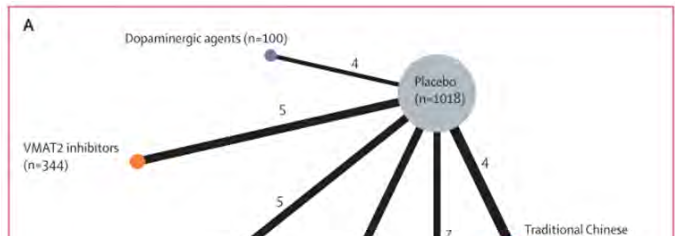
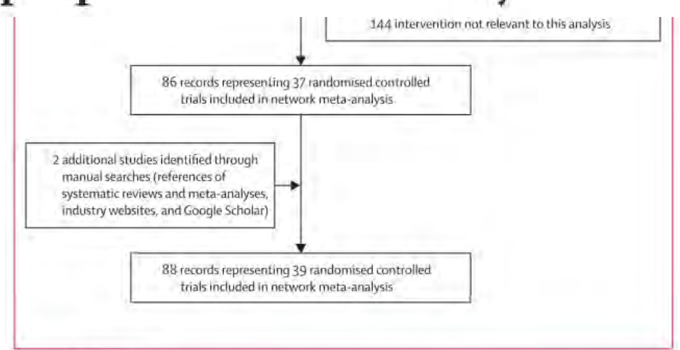




A Change in tic symptom severity (efficacy)

	Standardised mean difference (95% CI)
Metoclopramide	–1·11 (–1·93 to –0·29)
Ziprasidone	–1·10 (–1·93 to –0·27)
Ningdong	–0·96 (–1·48 to –0·44)
Xifeng Zhidong	–0·96 (–1·29 to –0·63)
Topiramate	–0·88 (–1·68 to –0·09)
Olanzapine	–0·83 (–1·49 to –0·18)
Changma Xifeng	–0·75 (–1·03 to –0·47)
Choudongning	–0·74 (–0·92 to –0·56)

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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Clonidine (n=384)
Guanfacine (n=28)
Haloperidol (n=98)
Pimozide (n=72)
Tiapride (n=470)
Aripiprazole (n=230)
Olanzapine (n=25)
Risperidone (n=111)
Ziprasidone (n=16)
5-Ling (n=362)
Changma Xifeng (n=328)
Choudongning (n=471)
Ningdong (n=33)
Xifeng Zhidong (n=79)
Ecopipam (n=93)

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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.

Effectiveness and safety of second-generation antipsychotics for psychiatric disorders apart from schizophrenia: A systematic review and meta-analysis

Xue-Zhu Feng [a,b], Zhe Li [c], Zi-Yi Li [d], Ke Wang [a], Xuan Tan [a,b], Yu-Yu Zhao [a,b], Wei-Feng Mi [e], Wei-Li Zhu [a], Yan-Ping Bao [a], Lin Lu [a,e,f,g,*], Su-Xia Li [a,*]

Psychiatry Research 332 (2024) 115637

Disorder	Drug	Comparison	Dose	n	N	Std. Mean Difference [95% CI]
Tourette's disorder	APZ	APZ vs PLB	5-20 mg/d	2	143	-0.80 [-1.14, -0.45]
	RIS	RIS vs PLB	0.5-6 mg/d	2	80	-0.71 [-1.16, -0.26]

Fig. 2. Pooled effect sizes of individual SGA on 11 disorders. QTP- quetiapine, LUR- lurasidone, RIS- risperidone, APZ- aripiprazole, OLZ- olanzapine, ZIP- ziprasidone, PALI- paliperidone, PLB- placebo, n- number of included studies, N- number of included participants, 95% CI- 95% confidence interval. * - one study had two dose subgroups of QTP, one was 300 mg/d and another was 300–800 mg/d.

3.2.8. *Tourette's disorder*

The pooled effect size showed a significant efficacy compared with placebo (4 studies, $N = 223$, effect size = -0.77, 95% CI: -1.04, -0.49; $p = 0.77$, $I^2 = 0\%$). APZ, 5–20 mg/d (Fig. 2), treatment duration of 8–12 w (Fig. S19), exhibited a greater significant efficacy compared with placebo (2 studies, $N = 143$, effect size = -0.80, 95% CI: -1.14, -0.45; $p = 0.41$, $I^2 = 0\%$) (Fig. S8).

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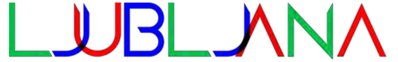

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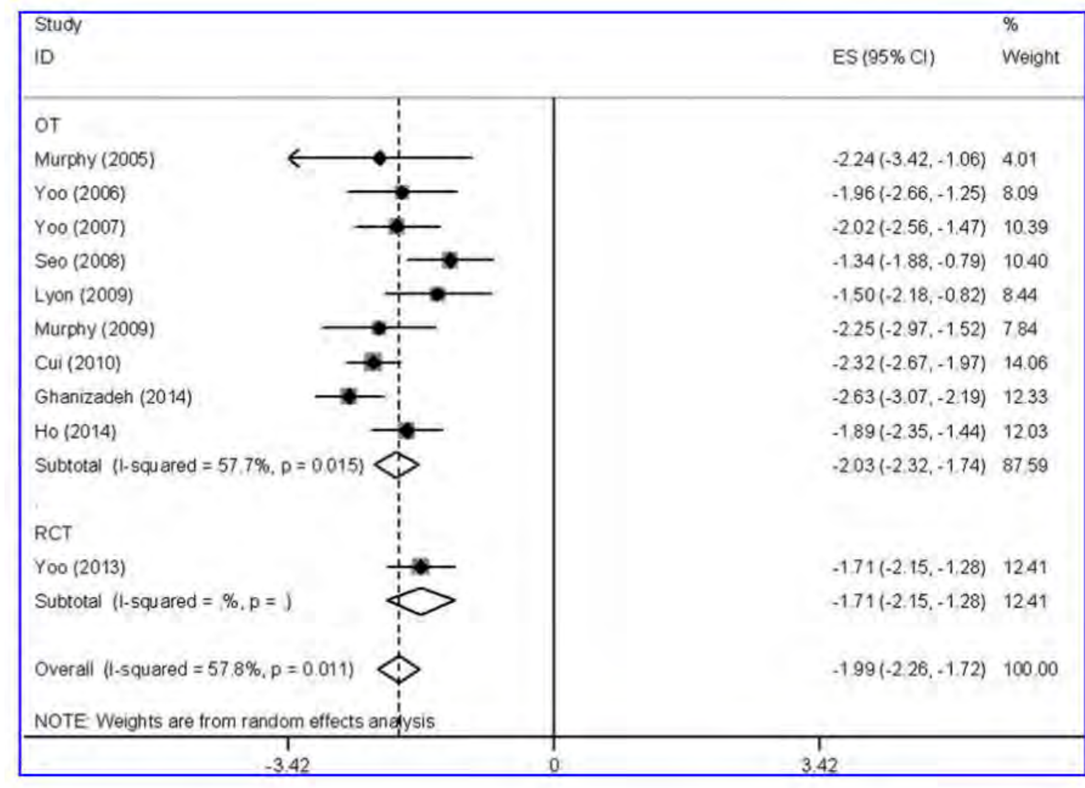
Original Article

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

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]

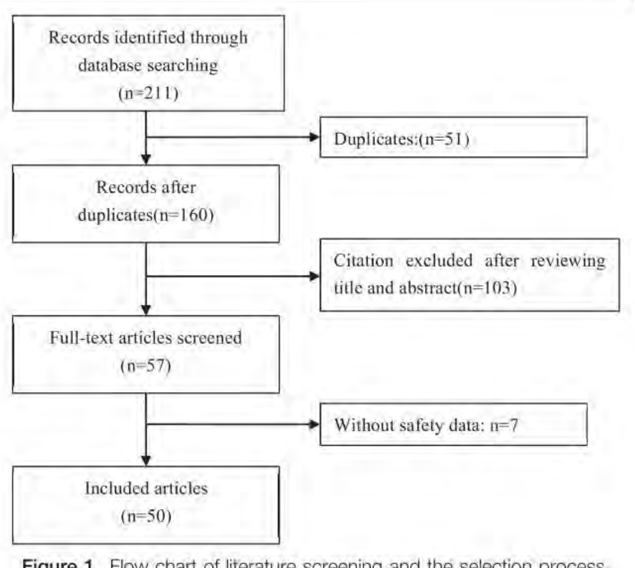


Figure 1. Flow chart of literature screening and the selection process.

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%).

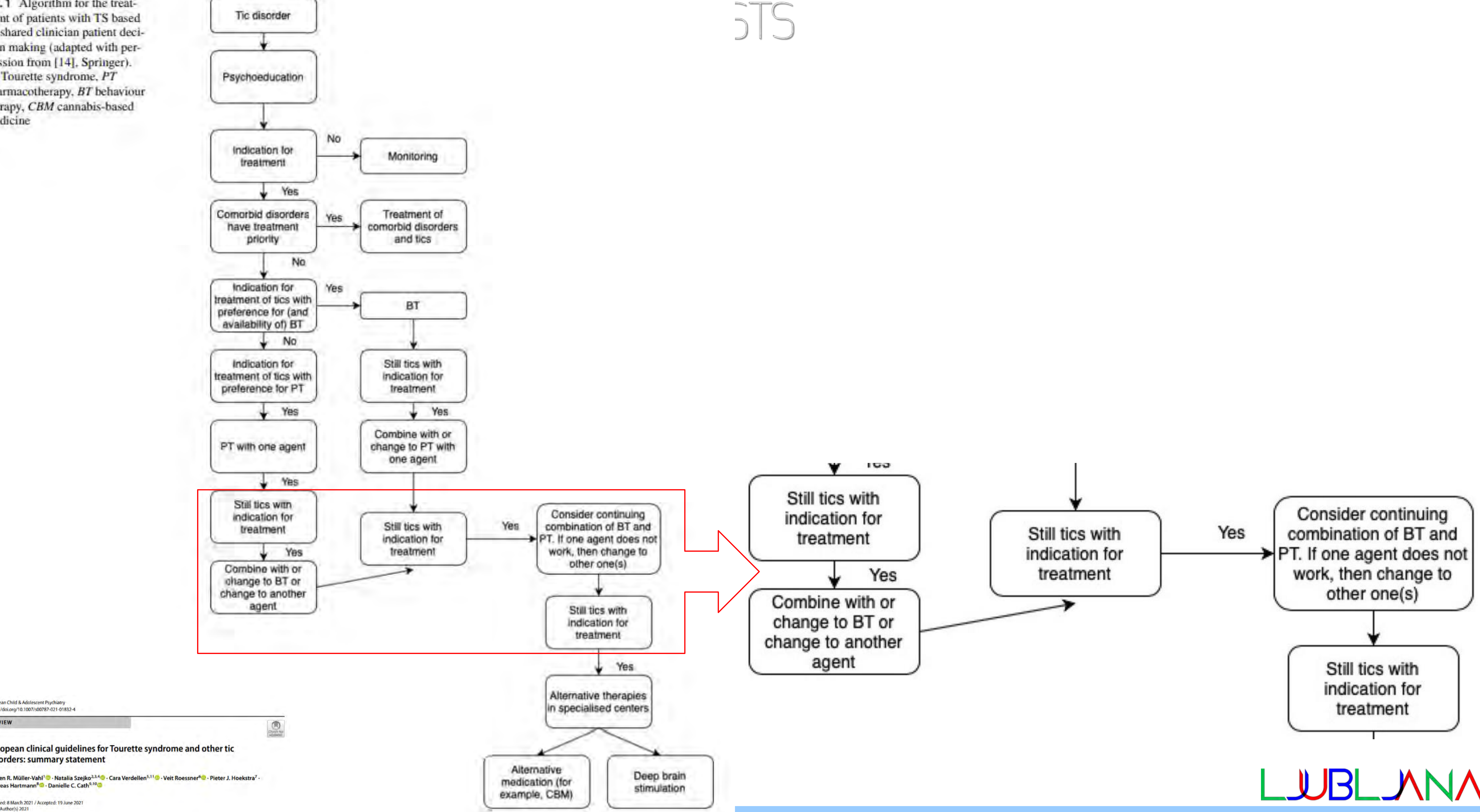


Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). TS Tourette syndrome, PT pharmacotherapy, BT behaviour therapy, CBM cannabis-based medicine
Tic disorder
Psychoeducation
Indication for treatment
No
Monitoring
Yes
Comorbid disorders have treatment priority
Yes
Treatment of comorbid disorders and tics
No
Indication for treatment of tics with preference for (and availability of) BT
Yes
BT
No
Indication for treatment of tics with preference for PT
Still tics with indication for treatment
Yes
PT with one agent
Combine with or change to PT with one agent
Still tics with indication for treatment
Combine with or change to BT or change to another agent
Still tics with indication for treatment
Yes
Consider continuing combination of BT and PT. If one agent does not work, then change to other one(s)
Still tics with indication for treatment
Alternative therapies in specialised centers
Alternative medication (for example, CBM)
Deep brain stimulation
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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]

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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
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ESSTS

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**

A Change in tic symptom severity (efficacy)

	Standardised mean difference (95% CI)
Metoclopramide	–1·11 (–1·93 to –0·29)
Ziprasidone	–1·10 (–1·93 to –0·27)
Ningdong	–0·96 (–1·48 to –0·44)
Xifeng Zhidong	–0·96 (–1·29 to –0·63)
Topiramate	–0·88 (–1·68 to –0·09)
Olanzapine	–0·83 (–1·49 to –0·18)
Changma Xifeng	–0·75 (–1·03 to –0·47)
Choudongning	–0·74 (–0·92 to –0·56)
Tiapride	–0·69 (–0·87 to –0·52)
Risperidone	–0·66 (–0·98 to –0·34)
Aripiprazole	–0·60 (–0·83 to –0·38)
5-Ling	–0·59 (–0·78 to –0·40)
Haloperidol	–0·51 (–0·88 to –0·14)
Pimozide	–0·48 (–0·84 to –0·12)
Ecopipam	–0·34 (–0·63 to –0·06)
Ondansetron	–0·24 (–1·00 to 0·52)
Guanfacine	–0·24 (–0·75 to 0·28)
Clonidine	–0·20 (–0·37 to –0·02)
Valbenazine	–0·14 (–0·37 to 0·08)
Pergolide	–0·08 (–0·58 to 0·43)
Deutetrabenazine	–0·02 (–0·27 to 0·23)
Pramipexole	0·00 (–0·53 to 0·53)
Levodopa	0·32 (–0·44 to 1·08)

–1·5 –1·0 –0·5 0 0·5 1·0 1·5

Moderate certainty of evidence · Low certainty of evidence · Very low certainty of evidence

A randomised, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome

J Jankovic,[1] J Jimenez-Shahed,[1] L W Brown[2]

J Neurol Neurosurg Psychiatry 2010;**81**:70–73. doi:10.1136/jnnp.2009.185348

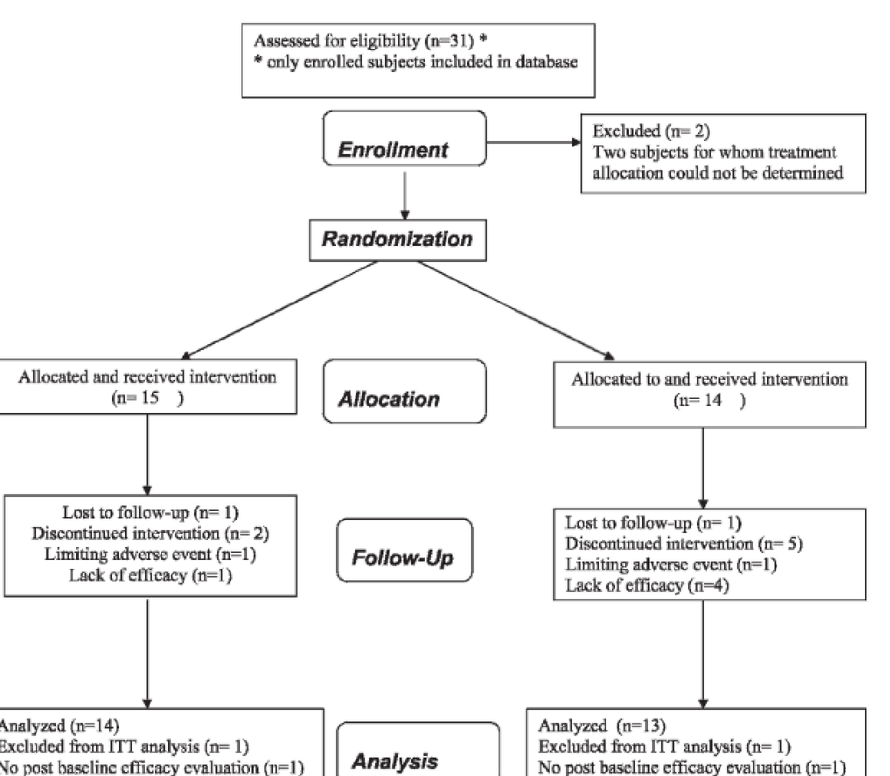

Table 2 Efficacy results (based on the intention-to-treat population)

Variable	Topiramate (N = 14)	Placebo (N = 13)	p Value	CI
Mean TTS (baseline)	26.64 (8.78)	28.77 (7.53)		
Mean TTS (visit 5)	12.36 (12.04)	23.10 (8.99)		−18.43 to −1.31
Mean change from baseline TTS (visit 5)*	−14.29 (10.47)	−5.00 (9.88)	0.0259	
Mean TMTS (baseline)	13.93 (4.70)	14.23 (4.21)		
Mean TMTS (visit 5)	8.14 (5.95)	12.80 (6.63)		−9.02 to −0.02
Mean change from baseline TMTS (visit 5)	−5.79 (5.67)	−1.30 (4.35)	0.0493	
Mean TPTS (baseline)	12.71 (5.36)	14.54 (5.38)		
Mean TPTS (visit 5)	4.21 (6.72)	10.30 (5.93)		−11.17 to −0.18
Mean change from baseline TPTS (visit 5)	−8.50 (6.10)	−3.70 (8.41)	0.0435	
Mean GSS (baseline)	57.36 (20.04)	58.00 (18.86)		
Mean GSS (visit 5)	20.21 (24.96)	50.10 (18.08)		−47.94 to −11.21
Mean change from baseline GSS (visit 5)	−37.14 (24.73)	−8.00 (22.48)	0.0030	

*A component of the Yale Global Tic Severity Scale, the change from baseline in Total Tic Score (TTS) at visit 5 (day 70) is the predefined primary endpoint
GSS, Global Severity Score; TMTS, Total Motor Tic Score; TPTS, Total Phonic Tic Score.

Results: There were 29 patients (26 males), mean age 16.5 (SD 9.89) years, randomised, and 20 (69%) completed the double-blind phase of the study. The primary endpoint was Total Tic Score, which improved by 14.29 (10.47) points from baseline to visit 5 (day 70) with topiramate (mean dose 118 mg) compared with a 5.00 (9.88) point change in the placebo group (p = 0.0259). There were statistically significant improvements also in the other components of the YGTSS as well as improvements in various secondary measures, including the CGI and premonitory urge CGI. No differences were observed in the frequency of adverse events between the two treatment groups.

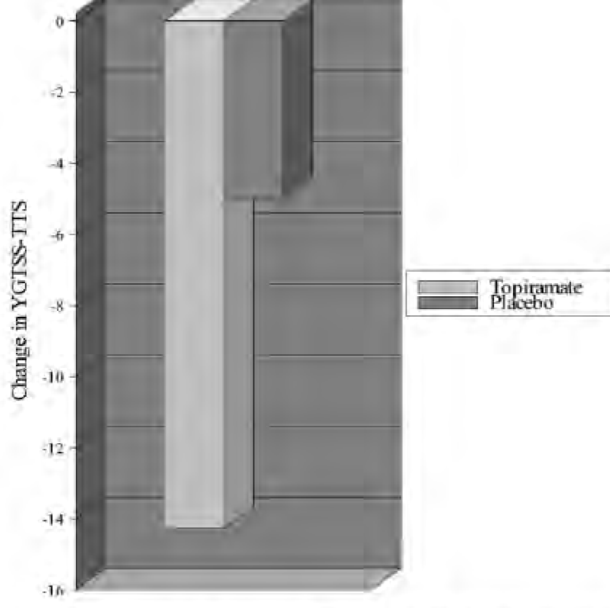

Figure 2 Change from baseline to visit 5 (day 70) in Total Tic Score component of Yale Global Tic Severity Scale (YGTSS-TTS) in response to topiramate.

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

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

MOVEMENT DISORDERS CLINICAL PRACTICE 2024. doi: 10.1002/mdc3.14296

TABLE 2 *Muscles injected for specific tics and onabotulinum toxin A (Botox) dosage*

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

Botulinum Toxin for the Treatment of Motor Tics in Children: A Case Series

Journal of Child Neurology
1-9
© The Author(s) 2025

Ethan Edmondson, MD[1], Mariam Hull, MD[1], Sukru Aras, PhD[2], and Mered Parnes, MD[1]

Table 2. Summary of Botulinum Neurotoxin Doses Administered.

Body Region	Site Injected	Average Dose and Range per Site (U)
Face	Frontalis	10
	Procerus	10
	Corrugator	12.3 [10-15]
	Upper eyelid	11 [10-12]
	Lateral canthus	8
	Lower eyelid	11 [10-12
	Nasalis	8
	Masseter	50
	Submental	47.5 [25-70]
Neck	Splenius capitis	66.7 [50-75]
	Scalene	42 [25-75]
	Sternocleidomastoid	46 [30-75]
Trunk	Trapezius	90 [50-125]
	Thoracic paraspinals	150
	Lumbar paraspinals	100
Upper extremity	Triceps	45
	Supinator	40
	Flexor carpi radialis	50
	Flexor carpi ulnaris	50
Lower extremity	Gluteus medius and gluteus minimus	100
	Extensor hallucis longus	80
	Flexor hallucis longus and brevis	60

“Overall, 64% of patients reported improvement in tic severity, 36% noted no change, and 6% worsened.”

STS

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

Tic disorder
Psychoeducation
Indication for treatment
No
Monitoring
Yes
Comorbid disorders have treatment priority
Yes
Treatment of comorbid disorders and tics
No
Indication for treatment of tics with preference for (and availability of) BT
Yes
BT
No
Indication for treatment of tics with preference for PT
Still tics with indication for treatment
Yes
PT with one agent
Yes
Combine with or change to PT with one agent
Yes
Still tics with indication for treatment
Yes
Combine with or change to BT or change to another agent
Still tics with indication for treatment
Yes
Consider continuing combination of BT and PT. If one agent does not work, then change to other one(s)
Still tics with indication for treatment
Yes
Alternative therapies in specialised centers
Alternative medication (for example, CBM)
Deep brain stimulation

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]

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Alternative medication (for example CBM = Cannabis-based medication)

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

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Primary Endpoint: 25% Tic Reduction (YGTSS-TTS) (n=97)

Rates and risk difference at EoT (week 10)
MANTEL-HAENSZEL-ESTIMATION stratified for center (primary Analysis)
ITT (according to study protocol)

Primary endpoint	**Nabiximols:** **n/N (%)**	**Placebo:** **n/N (%)**	**Mantel-Haenszel-Estimate of risk difference** **(Nabiximols-Placebo)** **[95%CI]** **pval**
25%-responder criterion	14/64 (21.88%)	3/33 (9.09%)	-0.1313 [-0.2756; 0.0129] 0.0742
30%-responder criterion	8/64 (12.50%)	1/33 (3.03%)	-0.0953 [-0.1928; 0.0022] 0.0555

Secondary Endpoint: Tic Change after 10 Weeks of Treatment compared to Baseline (YGTSS-TTS)

SEM-Plot YGTSS-TTS (Change from Baseline)

YGTSS-TTS

0
-2
-4

V02_Baseline
V04
V06
V08
V10
FUP

Visit

treatment ▲ Nabiximols ■ Placebo

LS Means (Nabiximols and placebo) derived from a MMRM.

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.

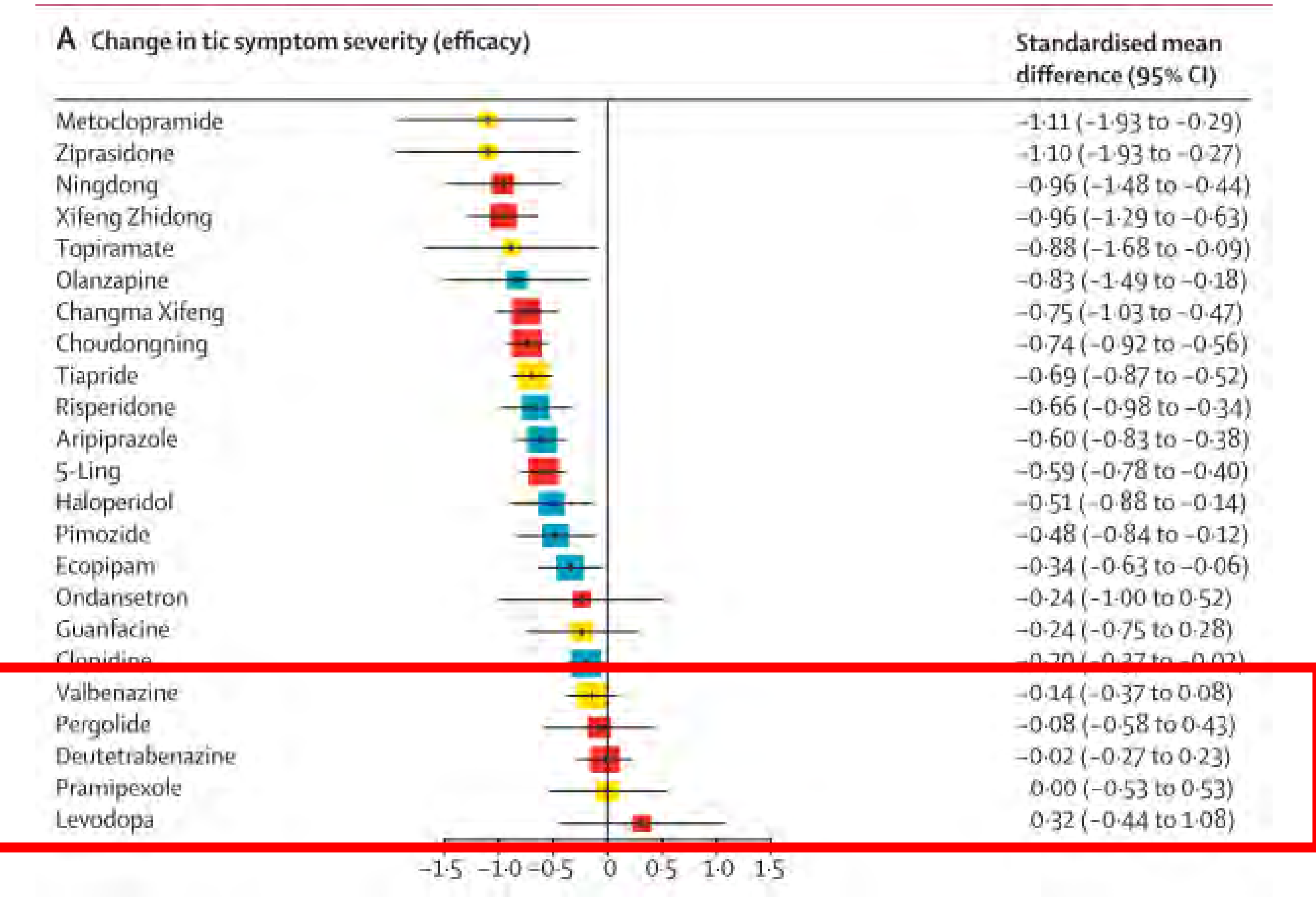
Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: a systematic review and network meta-analysis

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**

ESSTS

Negative Studies



Meta-Analysis: Efficacy and Tolerability of Vesicular Monoamine Transporter Type 2 Inhibitors in the Treatment of Tic Disorders

Emily Behling, MD Candidate,[1,2] Luis C. Farhat, MD,[3] Angeli Landeros-Weisenberger, MD,[1,4] and Michael H. Bloch, MD, MS[1,4*]

Movement Disorders, Vol. 37, No. 4, 2022

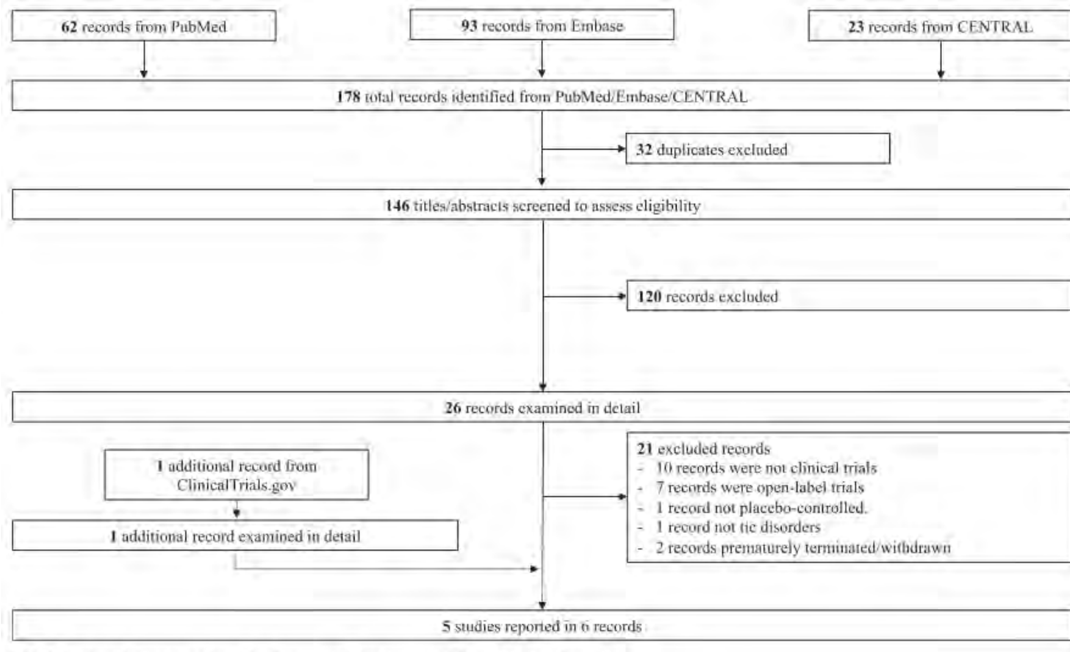


FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

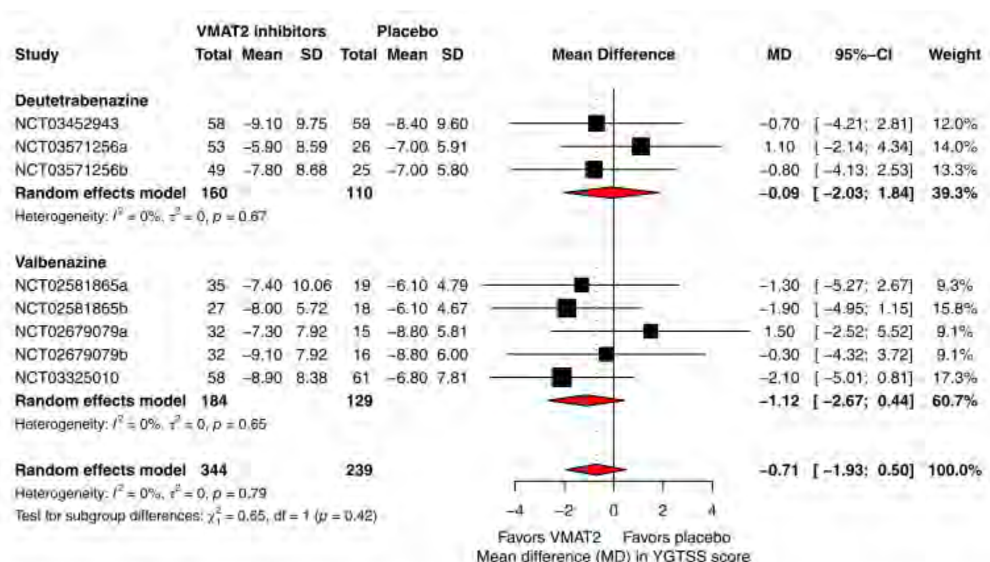


FIG. 2. Forest plot of change in tic symptom severity measured by the Yale Global Tic Symptom Severity Scale (YGTSS) stratified by medication. CI, confidence interval; SD, standard deviation; VMAT2, vesicular monoamine transporter type 2. [Color figure can be viewed at wileyonlinelibrary.com]

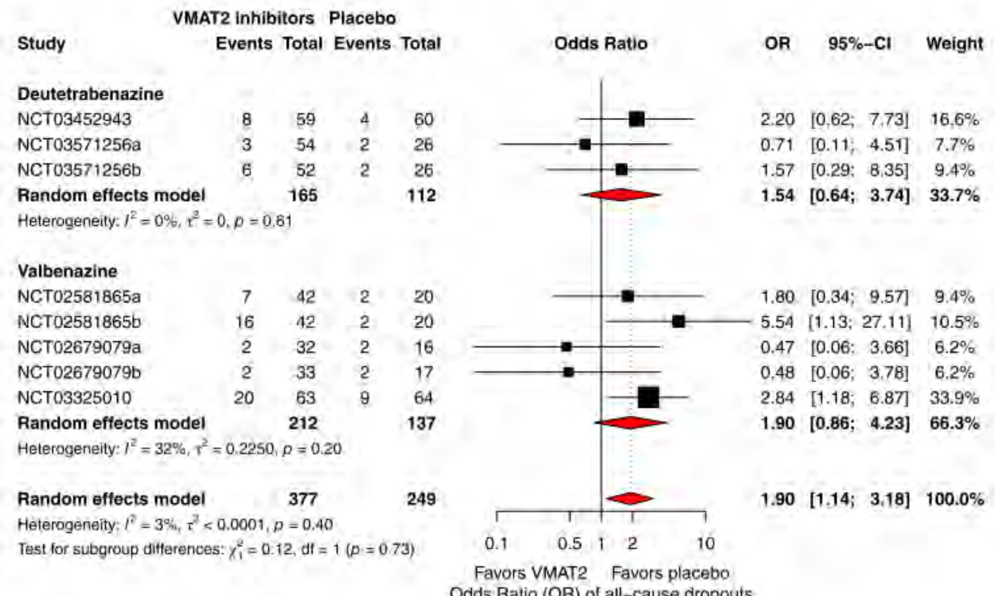


FIG. 3. Forest plot of dropout due to any reason stratified by medication. CI, confidence interval; VMAT2, vesicular monoamine transporter type 2. [Color figure can be viewed at wileyonlinelibrary.com]

Meta-Analysis: Efficacy and Tolerability of Vesicular Monoamine Transporter Type 2 Inhibitors in the Treatment of Tic Disorders

Emily Behling, MD Candidate,[1,2] Luis C. Farhat, MD,[3] Angeli Landeros-Weisenberger, MD,[1,4] and Michael H. Bloch, MD, MS[1,4*]

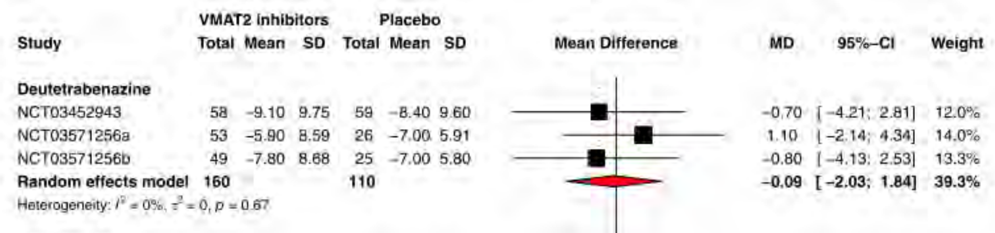
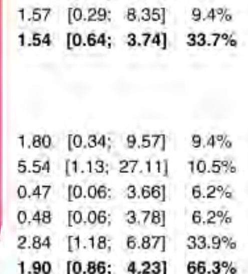


FIG. 1. Preferred Reporting Items f

ABSTRACT: Vesicular monoamine transporter type 2 (VMAT2) inhibitors may be an effective therapy for chronic tic disorders (CTD), including Tourette syndrome (TS), but there has not been a meta-analysis compiling available evidence from randomized controlled trials (RCTs). We performed a systematic review and meta-analysis to evaluate the efficacy, acceptability, and tolerability of VMAT2 inhibitors for CTD/TS. PubMed, CENTRAL, and Embase were searched for double-blinded RCTs of VMAT2 inhibitors versus placebo for the treatment of CTD/TS. Change in tic severity measured by the Yale Global Tic Severity Scale (efficacy) and rates of discontinuation attributed to adverse effects (tolerability) or all causes (acceptability) were extracted closest to 12 weeks. Mean difference (MD) and odds ratio (OR) were the effect size indexes for efficacy and acceptability/tolerability, respectively. Data were pooled through random-effects meta-analysis weighted by inverse variance. Five RCTs involving eight comparisons were included. Meta-analysis found a nonsignificant effect on efficacy ($k = 8$; N = 583; MD = −0.71; 95% confidence interval [CI], −1.93 to 0.50; $P = 0.24$), and there was certainty that the true effect is nonclinically meaningful (high quality of evidence). Meta-analysis found decreased tolerability ($k = 7$; N = 626; OR = 2.67; 95% CI, 1.21–5.92; $P = 0.01$) and decreased acceptability ($k = 8$; N = 626; OR = 1.90; 95% CI, 1.14–3.18; $P = 0.01$), although those comparisons were limited because of the relatively small number of events across trials. Meta-analyses did not support the efficacy of VMAT2 inhibitors in the short-term treatment of tic disorders and suggested no clinically meaningful effect of these agents on tic symptoms. © 2022 International Parkinson and Movement Disorder Society

Key Words: Tourette syndrome; tics; treatment; meta-analysis; vesicular monoamine transporter 2 (VMAT2)



Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.2250$, $p = 0.20$

Random effects model 377 249 — 1.90 [1.14; 3.18] 100.0%

Heterogeneity: $I^2 = 3\%$, $\tau^2 < 0.0001$, $p = 0.40$

Test for subgroup differences: $\chi^2_1 = 0.12$, df = 1 ($p = 0.73$)

Favors VMAT2 Favors placebo

Odds Ratio (OR) of all-cause dropouts

FIG. 3. Forest plot of dropout due to any reason stratified by medication. CI, confidence interval; VMAT2, vesicular monoamine transporter type 2. [Color figure can be viewed at wileyonlinelibrary.com]

SSTS

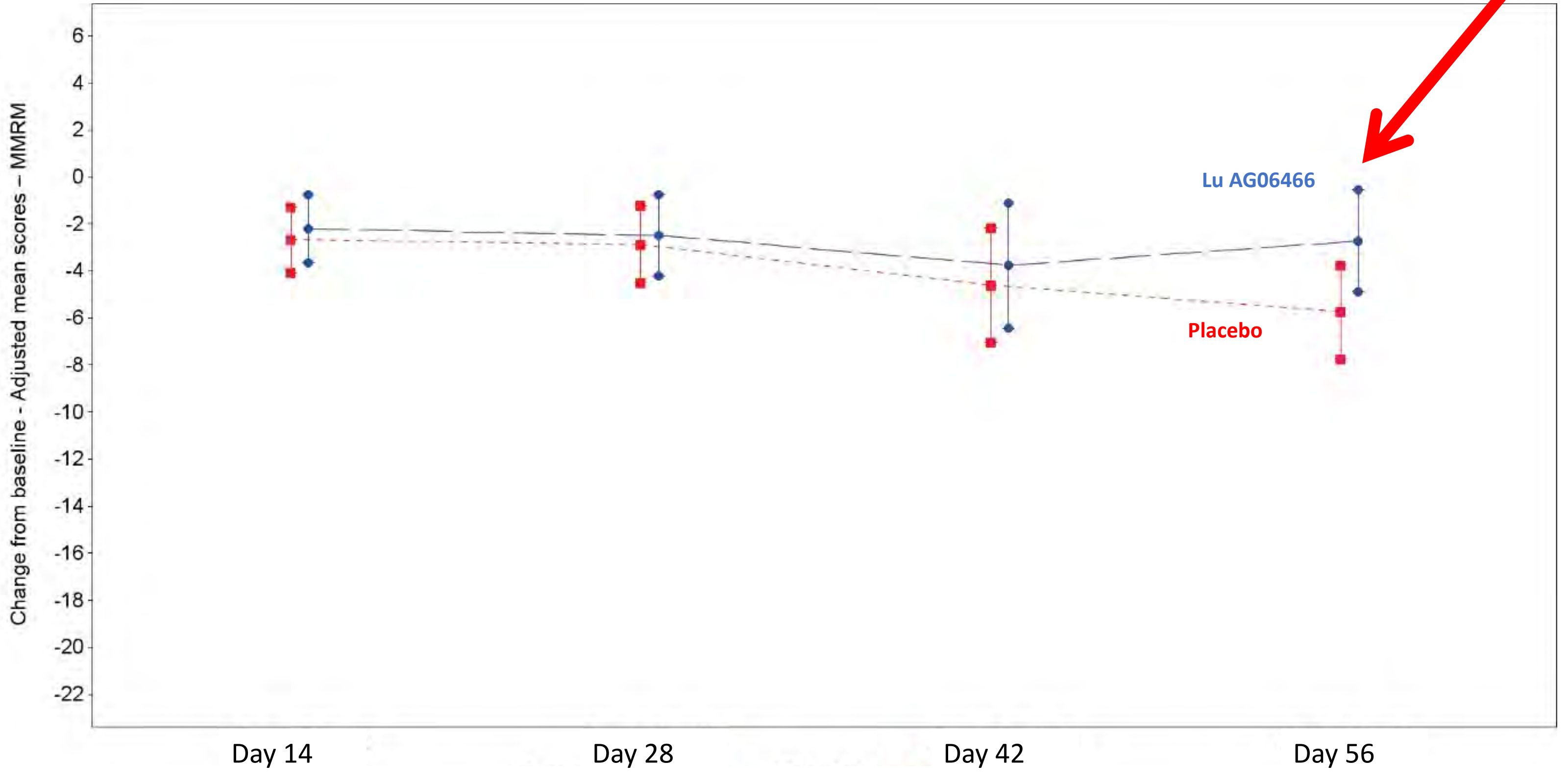
BRIEF REPORT | Open Access

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)



Placebo Effects in Tourette Syndrome

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

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

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

A Yale Global Tic Severity Scale-Total Tic Score

LS mean change ± SE from baseline: 0, -2, -4, -6, -8, -10, -12

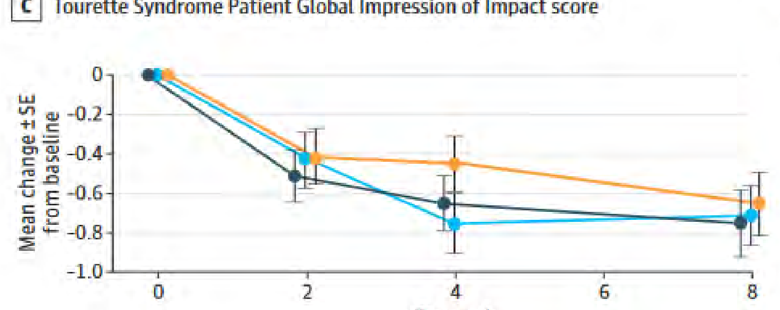
Time, wk: 0, 2, 4, 6, 8

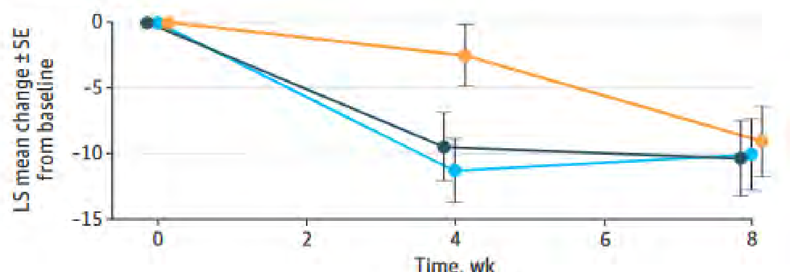
B Tourette Syndrome Clinical Global Impression score

LS mean change ± SE from baseline: 0, -0.2, -0.4, -0.6, -0.8, -1.0

Time, wk: 0, 2, 4, 6, 8

● Deutetrabenazine high dose ● Deutetrabenazine low dose ● Placebo

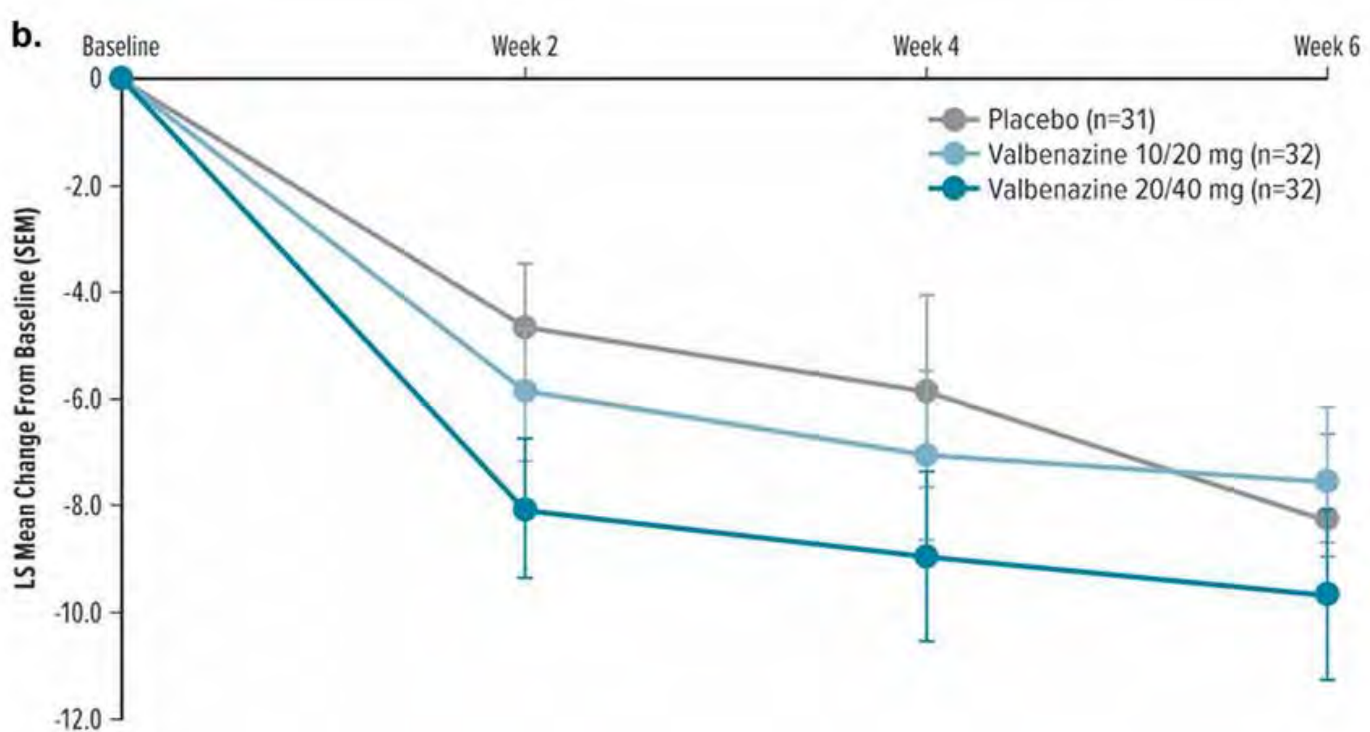




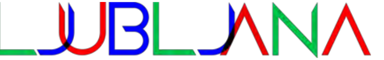
Clinical development of valbenazine for tics associated with Tourette syndrome

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.

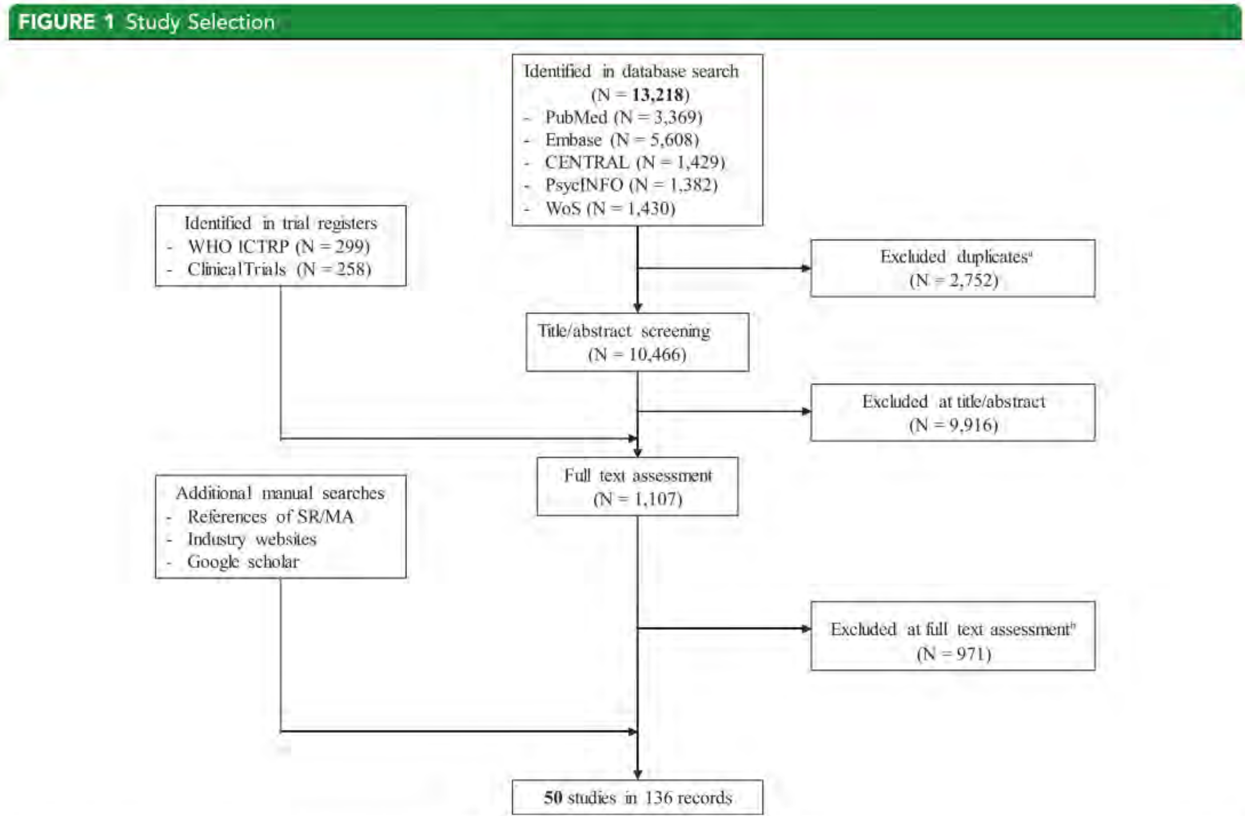


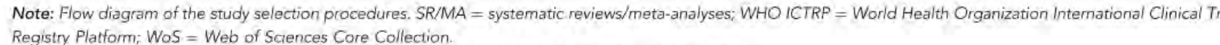
Systematic Review and Meta-Analysis: Placebo Response in Randomized Controlled Trials of Tourette's Disorder Medications

Pedro Macul Ferreira de Barros[a,†], MD, Luis C. Farhat[a,†], MD, PhD, Emily Behling[b], MD, Madeeha Nasir[b], MBBS, MS, Angeli Landeros-Weisenberger[b], MD, Michael H. Bloch[b,*], MD, MS

J Am Acad Child Adolesc Psychiatry 2025;64(5):577-592.

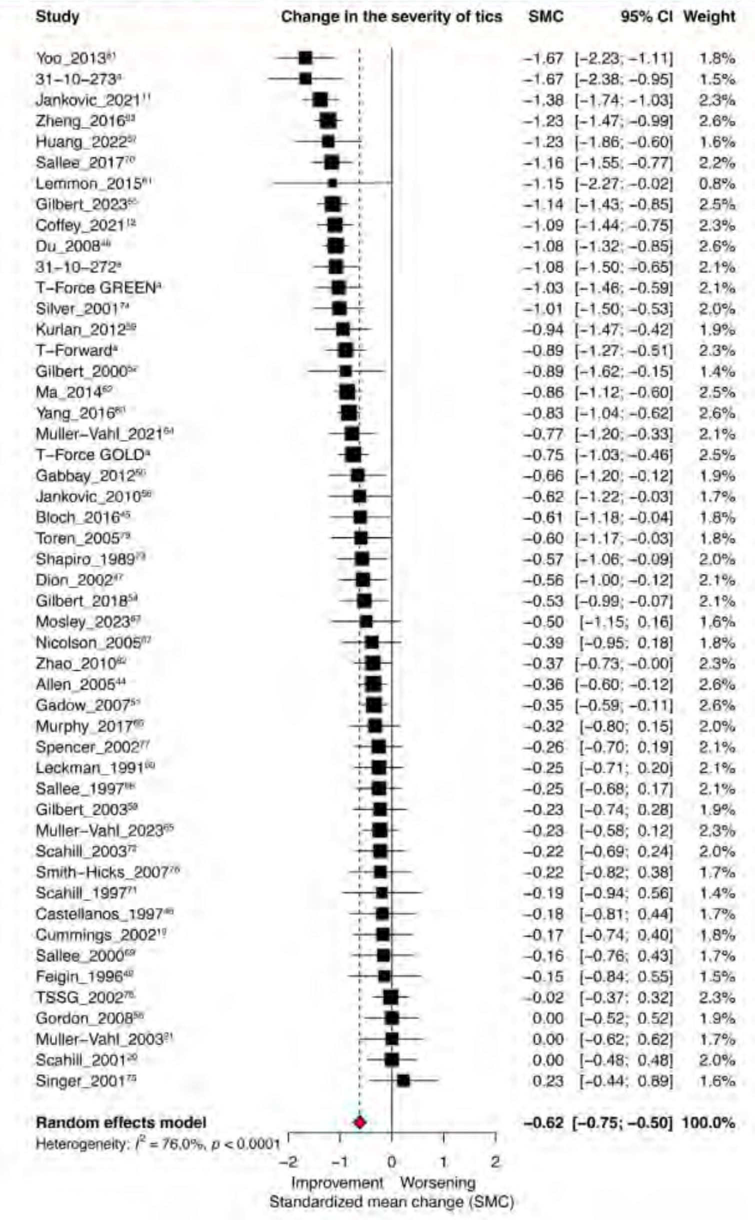
FIGURE 1 Study Selection





Note: Flow diagram of the study selection procedures. SR/MA = systematic reviews/meta-analyses; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform; WoS = Web of Sciences Core Collection.
[a]The reasons for exclusion for each individual record are outlined in Supplement 5, available online.
[b]Main reasons for exclusion were "not tic disorders," "not clinical trial," and "not pharmacological intervention."

FIGURE 2 Change in Tics Severity During Treatment With Placebo



Note: Forest plot for the main meta-analysis. Results from individual studies are illustrated as black squares and correspond to values of standardized mean change (SMC) alongside 95% CI. The estimate from random-effects meta-analysis weighted by the inverse of the variance is illustrated as the red diamond. Values to the left of the reference line indicate improvement, whereas values to the right indicate worsening, during treatment with placebo. Please note color figures are available online.

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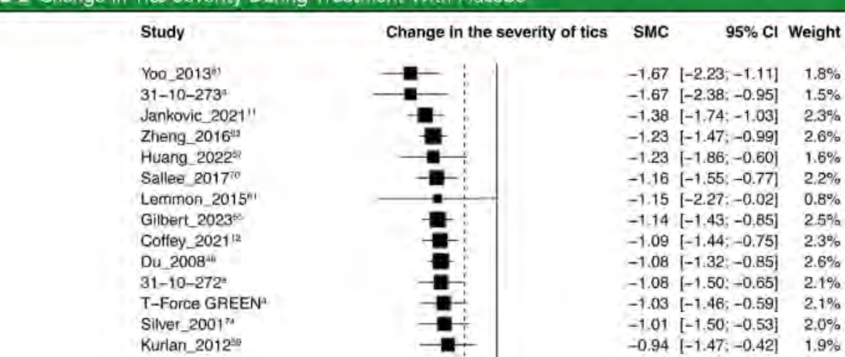
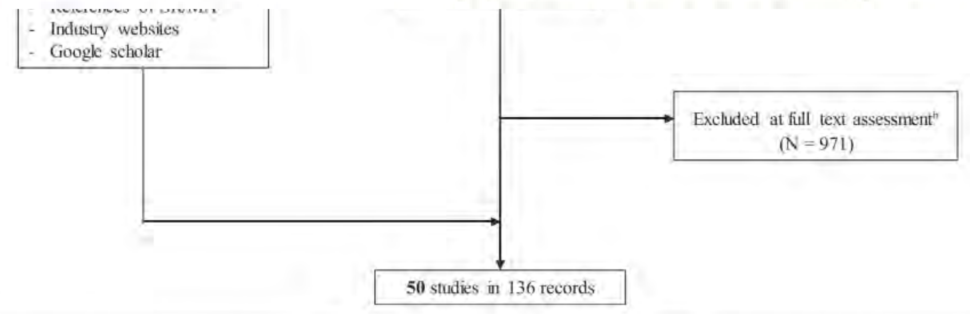


Results: Literature searches identified 13,775 records, and 50 RCTs involving 1,566 participants were included in the placebo meta-analysis. Placebo response was medium to large (standardized mean change: −0.62; 95% CI: −0.75, −0.5; $I^2 = 76\%$; $\tau^2 = 0.14$). Several factors were associated with larger placebo responses (eg, non-US RCT, industry sponsorship, number of centers and participants). However, there was a moderate-to-high correlation between placebo and drug response (ρ = 0.66; 95% CI: 0.47, 0.79), and factors associated with larger placebo response were also generally associated with larger drug responses. There was not a significant correlation between placebo response and drug-placebo differences (ρ = −0.05; 95% CI: −0.32, 0.22), and factors associated with larger placebo response generally did not interfere in drug-placebo differences.

Conclusion: The magnitude of placebo response in Tourette's disorder may be large, but similar to that in other child and adolescent psychiatric conditions. Clinical researchers may manipulate study-level factors to diminish placebo response (eg, carefully selecting study sites and keeping them at the minimum feasibility). However, drug-placebo differences may not increase as drug response will likely diminish as well.



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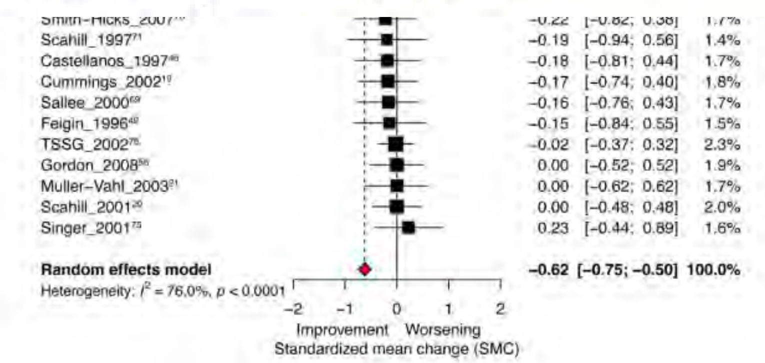

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Promising new Treatments

THERAPEUTIC ADVANCES in
Neurological Disorders

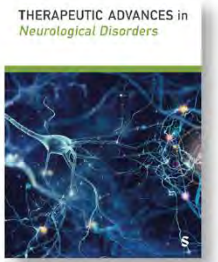
Plain Language Summary of Publication

ESSTS

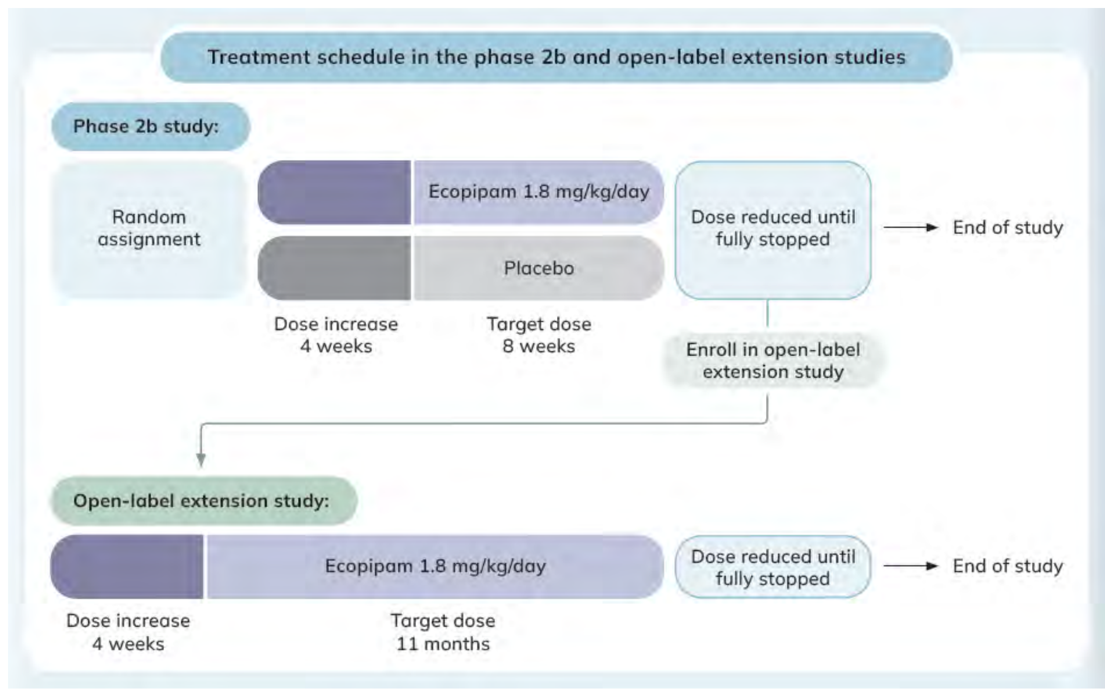
Plain Language Summary of a Phase 2b Randomized Controlled Trial of Ecopipam and Its 12-Month Open-Label Extension in Children and Adolescents With Tourette Syndrome

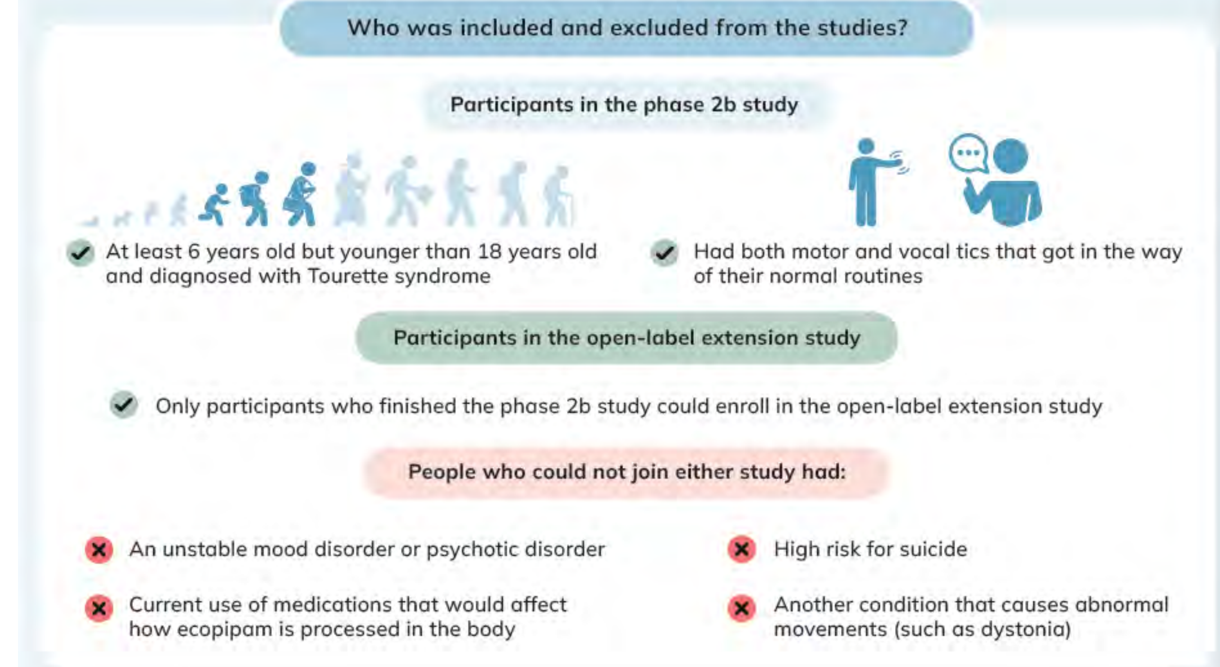
Donald L. Gilbert[1,2]; David J. B. Kim[3]; Meredith M. Miller[3]; Sarah D. Atkinson[3]; George B. Karkanias[3]; Frederick E. Munschauer[3]; Stephen P. Wanaski[4]; Timothy M. Cunniff[4]

Received: 14 January 2026; Revised article accepted: 30 January 2026



Phase 2b study: n=153
N=121 who finished the phase 2b study were then treated with ecopipam in the open-label extension study





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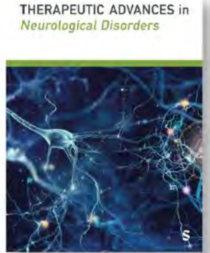
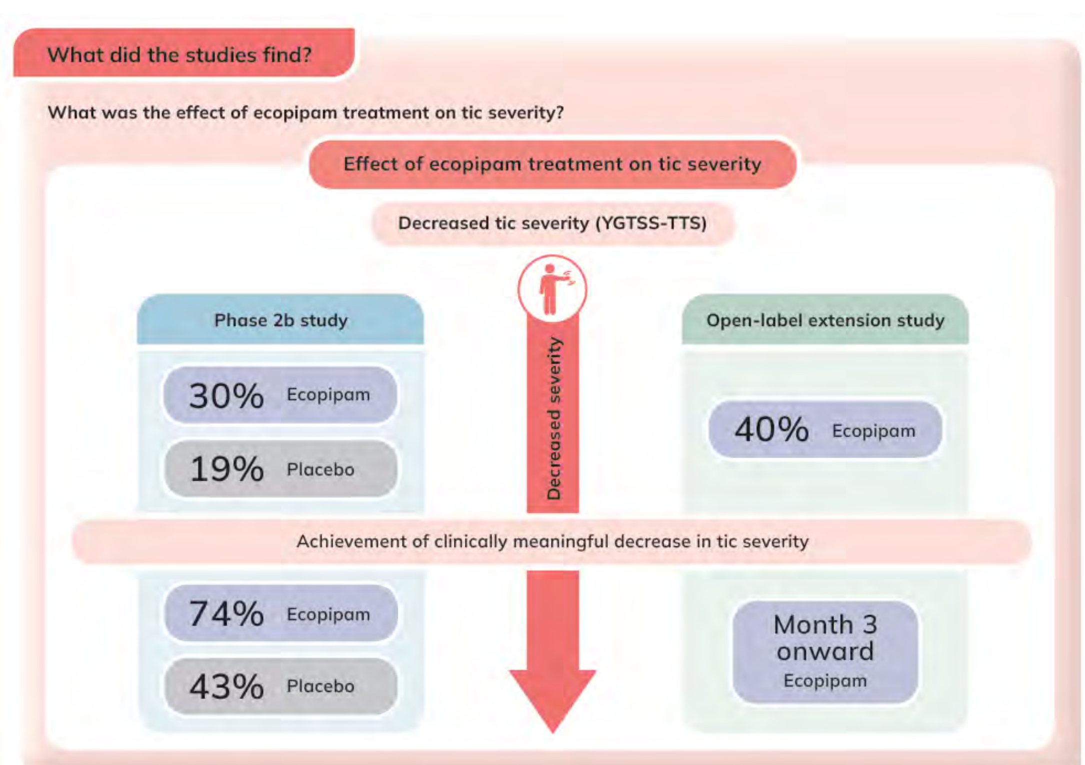
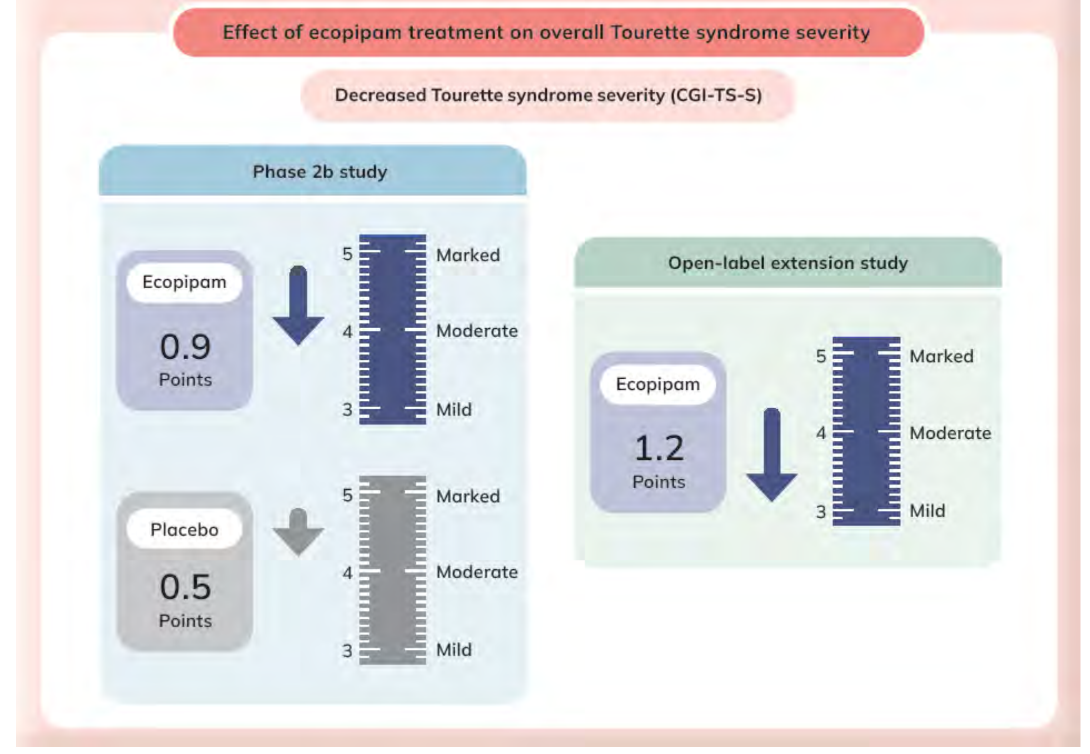


Significant tic reduction (YGTSS-TTS)
Significant overall improvement (CGI-TS-S)





THERAPEUTIC ADVANCES in
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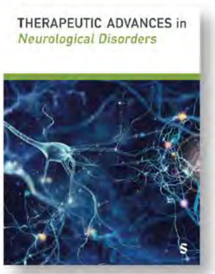


Donald L. Gilbert[1,2]; David J. B. Kim[3]; Meredith M. Miller[3]; Sarah D. Atkinson[3]; George B. Karkanias[3]; Frederick E. Munschauer[3]; Stephen P. Wanaski[4]; Timothy M. Cunniff[4]

Received: 14 January 2026; Revised article accepted: 30 January 2026

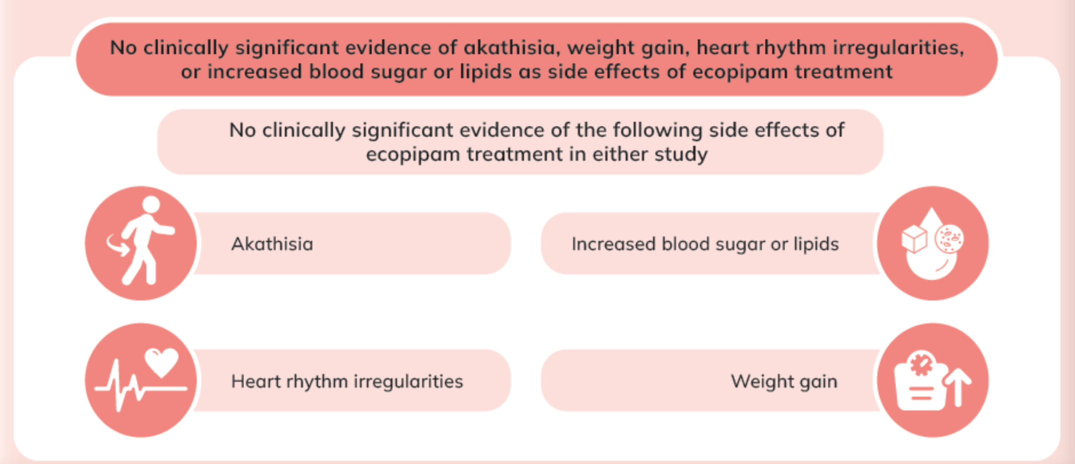
What were the side effects of ecopipam treatment?

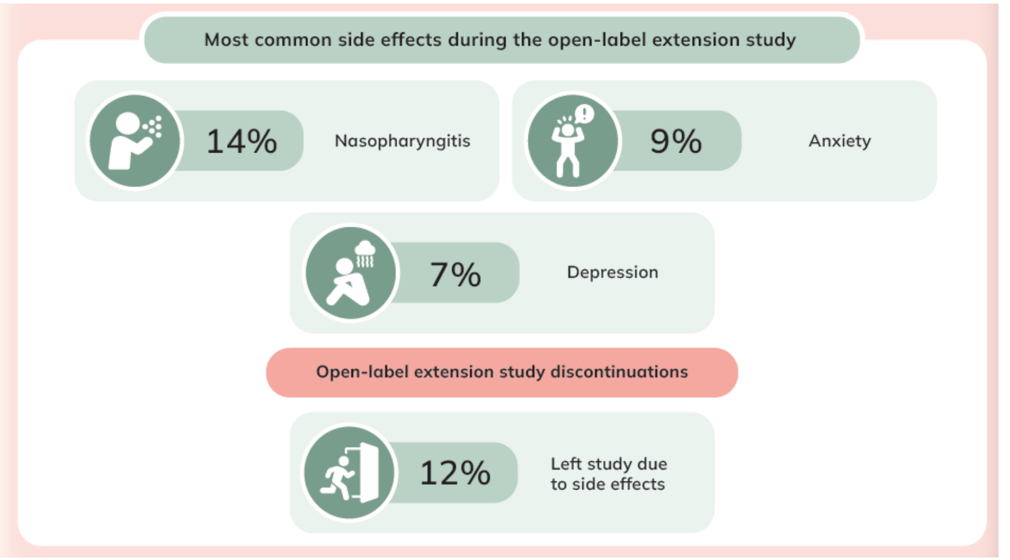
Most common side effects during the phase 2b study

Side effect	Ecopipam	Placebo
Headache	16%	9%
Insomnia	13%	3%
Fatigue	8%	0%
Somnolence	8%	3%

Phase 2b study discontinuations

Side effect	Ecopipam	Placebo
Left study due to side effects	5%	1%





Safety and Efficacy of Ecopipam in Patients with Tourette Syndrome: A Systematic Review and Meta-analysis

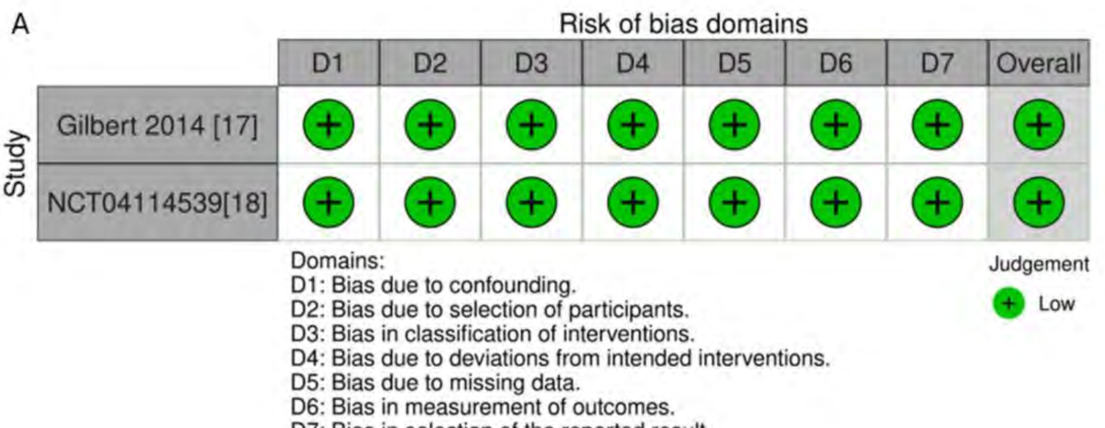
ESSTS

Prateek Kumar Panda[1] · Pragnya Panda[2] · Lesa Dawman[3] · Anand Santosh Mishra[1] · Vinod Kumar[4] · Indar Kumar Sharawat[1]

CNS Drugs
https://doi.org/10.1007/s40263-024-01140-w

Low Risk of Bias

Fig. 2 Risk of bias summary of included nonrandomized studies of interventions (**A**) and randomized controlled trials (**B**)



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Significant improvement of Tics

A

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	30.6	8.8	18	25.3	9.2	18	5.8%	5.30 [-0.58, 11.18]
Gilbert 2018 [12]	32.8	7.1	40	27.2	9.1	40	15.7%	5.60 [2.02, 9.18]
Gilbert 2023 [11]	34.7	5.6	75	25.9	4.3	75	78.5%	8.80 [7.20, 10.40]
Total (95% CI)			**133**			**133**	**100.0%**	**8.10 [6.68, 9.51]**

Heterogeneity: Chi² = 3.48, df = 2 (P = 0.18); I² = 43%
Test for overall effect: Z = 11.21 (P < 0.00001)

B

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	16.2	4.5	18	13.7	4.2	18	28.7%	2.50 [-0.34, 5.34]
Gilbert 2018 [12]	18.4	3.3	40	15.1	4.8	40	71.3%	3.30 [1.49, 5.11]
Total (95% CI)			**58**			**58**	**100.0%**	**3.07 [1.55, 4.59]**

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 3.95 (P < 0.0001)

C

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	14.4	5.9	18	11.6	6.8	18	22.4%	2.80 [-1.36, 6.96]
Gilbert 2018 [12]	14.4	4.9	40	12.2	5.3	40	77.6%	2.20 [-0.04, 4.44]
Total (95% CI)			**58**			**58**	**100.0%**	**2.33 [0.36, 4.30]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

D

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	4.7	1	18	3.9	1.2	18	7.6%	0.80 [0.08, 1.52]
Gilbert 2018 [12]	4.5	0.7	40	3.7	1	40	27.7%	0.80 [0.42, 1.18]
Gilbert 2023 [11]	4.8	0.8	71	3.9	0.7	71	64.7%	0.90 [0.65, 1.15]
Total (95% CI)			**129**			**129**	**100.0%**	**0.86 [0.67, 1.06]**

Heterogeneity: Chi² = 0.22, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 8.52 (P < 0.00001)

Fig. 3 Pooled estimate for change in YGTSS-TS-total score (**A**), YGTSS-TS-motor score (**B**), YGTSS-TS-phonic score (**C**), and Clinical Global Impression-TS-severity score before and after administration of ecopipam. *YGTSS-TS* Global Tic Severity Scale-Tourette syndrome, *SD* standard deviation, *CI* confidence interval, *IV* inverse variance

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https://doi.org/10.1007/s40263-024-01140-w

Significant improved CGI-TS-I

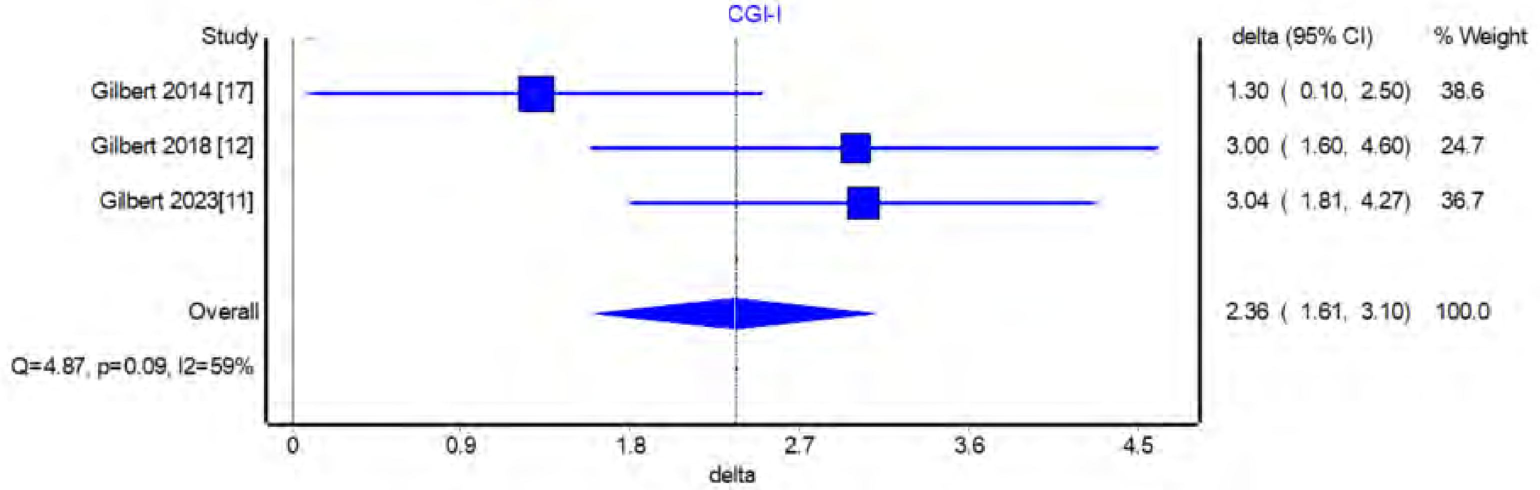

Fig. 4 The clinical global impression-Tourette syndrome-improvement score after administering ecopipam. *CGI-I* clinical global impression-improvement, *CI* confidence interval

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CNS Drugs
https://doi.org/10.1007/s40263-024-01140-w

No change in depressive, OCD, or ADHD symptoms

A

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	3.1	2.3	18	3.4	3.1	18	13.7%	-0.11 [-0.76, 0.55]
Gilbert 2018 [12]	54.7	9.9	40	54	9.6	40	30.4%	0.07 [-0.37, 0.51]
Gilbert 2023 [11]	28.1	10	74	25.6	8.8	74	55.9%	0.26 [-0.06, 0.59]
Total (95% CI)			**132**			**132**	**100.0%**	**0.15 [-0.09, 0.40]**

Heterogeneity: Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)

B

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	7.8	8	18	8.1	7.5	18	11.2%	-0.30 [-5.37, 4.77]
Gilbert 2018 [12]	5.7	6.3	40	5	6.1	40	38.7%	0.70 [-2.02, 3.42]
Gilbert 2023 [11]	5.7	7.9	74	4.5	6.9	74	50.1%	1.20 [-1.19, 3.59]
Total (95% CI)			**132**			**132**	**100.0%**	**0.84 [-0.85, 2.53]**

Heterogeneity: Chi² = 0.29, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

C

Study or Subgroup	Pre-intervention Mean	SD	Total	Post-intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gilbert 2014 [17]	14.4	5.9	18	11.6	6.8	18	22.4%	2.80 [-1.36, 6.96]
Gilbert 2018 [12]	14.4	4.9	40	12.2	5.3	40	77.6%	2.20 [-0.04, 4.44]
Total (95% CI)			**58**			**58**	**100.0%**	**2.33 [0.36, 4.30]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

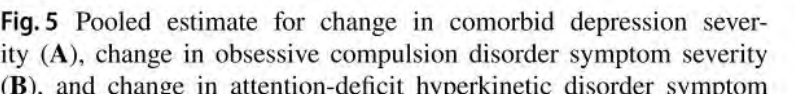

Fig. 5 Pooled estimate for change in comorbid depression severity (**A**), change in obsessive compulsion disorder symptom severity (**B**), and change in attention-deficit hyperkinetic disorder symptom severity (**C**) before and after administration of ecopipam. *SD* standard deviation, *CI* confidence interval, *IV* inverse variance

Safety and Efficacy of Ecopipam in Patients with Tourette Syndrome: A Systematic Review and Meta-analysis

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CNS Drugs
https://doi.org/10.1007/s40263-024-01140-w

AEs comparable to Placebo

- Incidence of adverse effects comparable in the ecopipam and placebo group:
  - headache, vomiting, somnolence, and fatigue (p = 0.24, 0.24, 0.11, and 0.05; I2 = 0%, 0%, 0%, and 46%, respectively)
- Only insomnia was more frequent in the ecopipam group (p = 0.009, I2 = 0%)
- Frequency of adverse events leading to withdrawal of study medication or severe adverse effects were also comparable in both groups (p = 0.10, 0.51; I2 = 0%, 39%, respectively)

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https://doi.org/10.1007/s40263-024-01140-w

Efficacy of ecopipam similar to pimozide

- Reduction in YGTSS-TTS compared to other after FDA-approved drugs
  - Ecopipam: −8.1 points
  - Pimozide: −9.1 points
  - Haloperidol: −16.5 points
  - Aripiprazole: −14.4 points

Based on an extrapolation from previous trials

- Gilbert et al. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. J Am Acad Child Adolesc Psychiatry. 2004;43:206–14
- Yoo et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. Eur Child Adolesc Psychiatry. 2011;20:127–35

LJUBLJANA

JAMA Neurology | Original Investigation

Efficacy and Safety of Ecopipam for Tourette Syndrome
A Phase 3 Randomized Clinical Trial

Donald L. Gilbert, MD, MS; Sarah D. Atkinson, MD; David J. B. Kim, BS; Meredith M. Miller, BS; Patricia M. Rice, MS; John A. Flatt, MD; George B. Karkanias, PhD, MBA; Frederick E. Munschauer, MD; Richard M. Bittman, PhD; Stephen P. Wanaski, PhD; Timothy M. Cunniff, PharmD; Kinga K. Tomczak, MD, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2026.1431
Published online May 26, 2026.

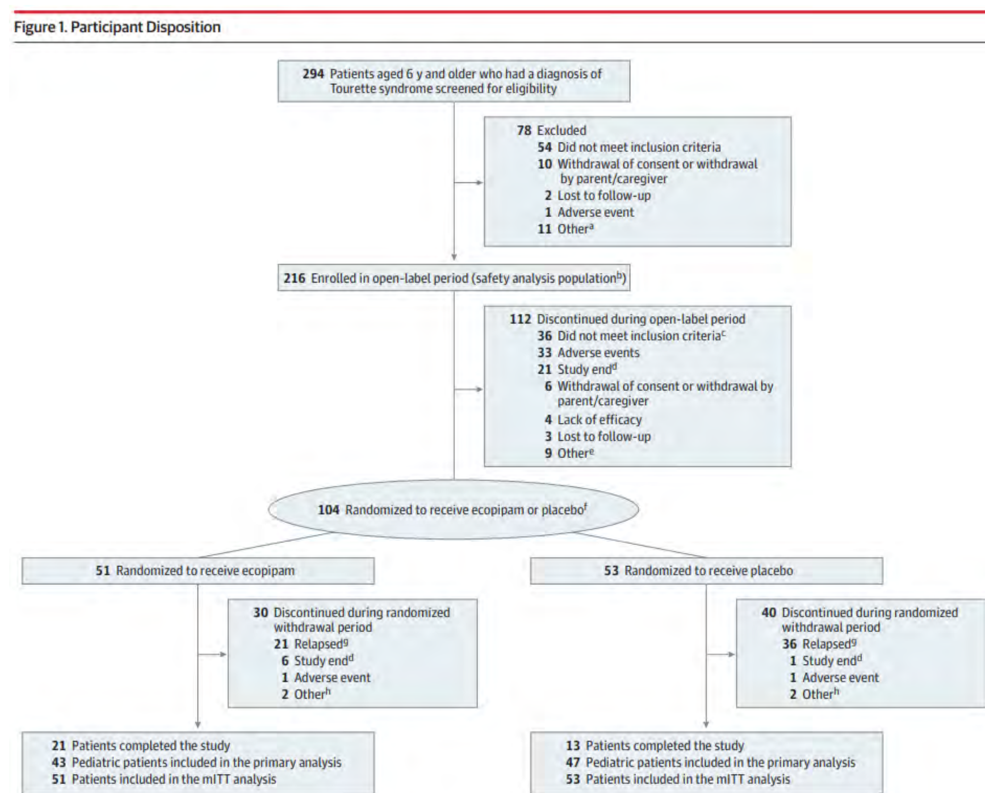
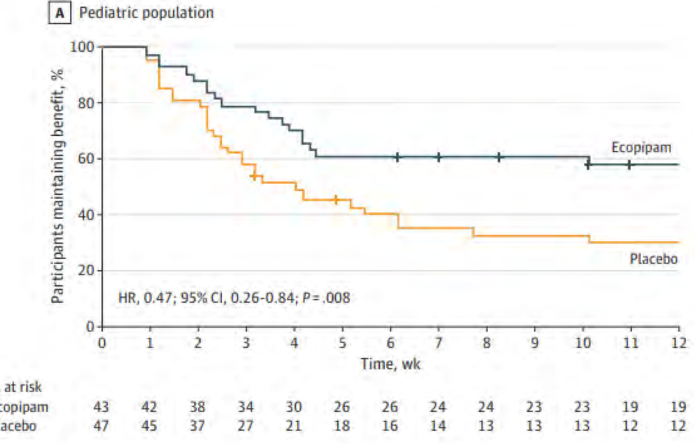
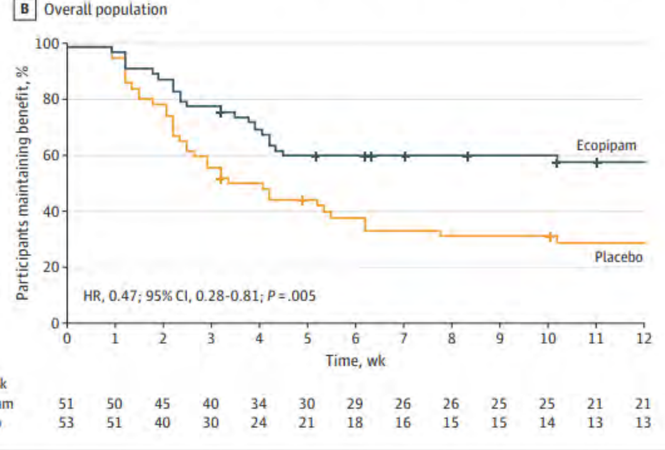


Figure 1. Participant Disposition

Figure 2. Kaplan-Meier Curves for Time to Relapse in the Pediatric Population (A) and Overall Population (B) From Randomization (Week 12)





The plus (+) sign indicates censored data. Relapse was defined as ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score previously observed from baseline to week 12, initiation of additional medications for Tourette syndrome symptoms, or hospitalization related to worsening symptoms. HR indicates hazard ratio.

JAMA Neurology | Original Investigation

Efficacy and Safety of Ecopipam for Tourette Syndrome
A Phase 3 Randomized Clinical Trial

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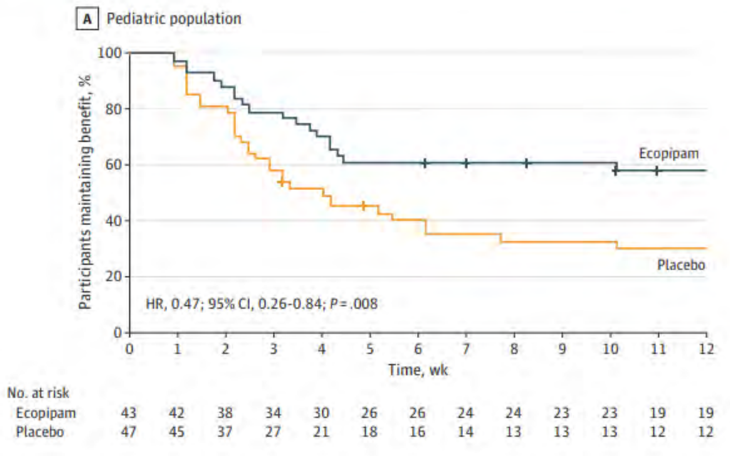
JAMA Neurol. doi:10.1001/jamaneurol.2026.1431
Published online May 26, 2026.

Significant improvement of Tics

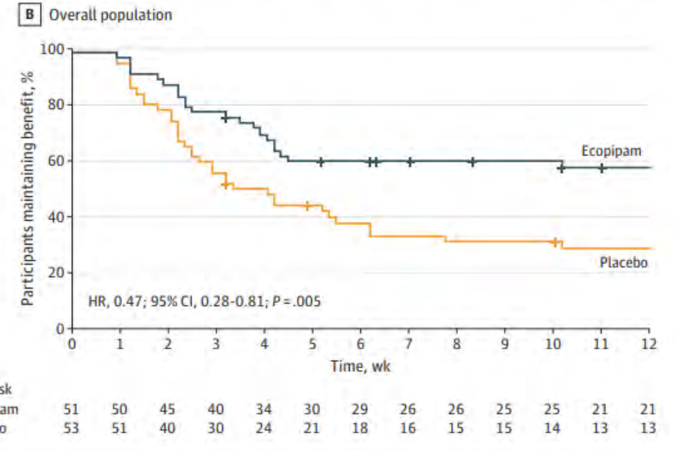
Findings This randomized clinical trial included a 12-week open-label period and a 12-week double-blind, randomized withdrawal period for individuals with clinically meaningful tic reduction. Ecopipam was well tolerated and significantly reduced the probability of relapse in pediatric participants.

Meaning Ecopipam induced and maintained a clinically meaningful reduction in severity of tics for up to 24 weeks.

Figure 2. Kaplan-Meier Curves for Time to Relapse in the Pediatric Population (A) and Overall Population (B) From Randomization (Week 12)



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Ecopipam	43	42	38	34	30	26	26	24	24	23	23	19	19
Placebo	47	45	37	27	21	18	16	14	13	13	13	12	12



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Ecopipam	51	50	45	40	34	30	29	26	26	25	25	21	21
Placebo	53	51	40	30	24	21	18	16	15	15	14	13	13

The plus (+) sign indicates censored data. Relapse was defined as ≥50% loss of improvement in Yale Global Tic Severity Scale Total Tic Score previously observed from baseline to week 12, initiation of additional medications for Tourette syndrome symptoms, or hospitalization related to worsening symptoms. HR indicates hazard ratio.

JAMA Neurology | Original Investigation

ESSTS

Efficacy and Safety of Ecopipam for Tourette Syndrome

A Phase 3 Randomized Clinical Trial

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Ecopipam well tolerated

Table 3. Summary of Adverse Events

Adverse event	No. (%) Open-label period Ecopipam (n = 216)	Double-blind period Ecopipam (n = 51)	Double-blind period Placebo (n = 53)	All periods Ecopipam (n = 216)
Any AE	140 (64.8)	20 (39.2)	22 (41.5)	147 (68.1)
Treatment-related AE	90 (41.7)	7 (13.7)	8 (15.1)	92 (42.6)
Severe AE	12 (5.6)	0	2 (3.8)	12 (5.6)
Serious AE[a]	1 (0.5)	1 (2.0)	2 (3.8)	2 (0.9)
Treatment discontinuation due to AE	34 (15.7)	0[b]	1 (1.9)[c]	34 (15.7)
Most frequently reported AEs[d]				
Somnolence	24 (11.1)	0	0	24 (11.1)
Anxiety	20 (9.3)	1 (2.0)	1 (1.9)	21 (9.7)
Headache	19 (8.8)	2 (3.9)	3 (5.7)	21 (9.7)
Insomnia	16 (7.4)	3 (5.9)	5 (9.4)	19 (8.8)
Tic	15 (6.9)	2 (3.9)	1 (1.9)	17 (7.9)
Fatigue	14 (6.5)	0	0	14 (6.5)
Select AEs of special interest[e]				
Anxiety-related	20 (9.3)	1 (2.0)	1 (1.9)	21 (9.7)
Depression-related	14 (6.5)	0	2 (3.8)	14 (6.5)
Suicidal ideation	5 (2.3)	0	1 (1.9)[c]	5 (2.3)
Drug-induced movement disorder-related	0[e]	0	0	0[e]

Abbreviation: AE, adverse event.

[a] Open-label ecopipam: 1 participant with acute kidney injury, blood creatine phosphokinase increased, and obsessive-compulsive disorder (all considered possibly or probably related to treatment); double-blind ecopipam: 1 participant with type 1 diabetes; double-blind placebo: suicidal ideation (considered possibly related to treatment) and Tourette syndrome in 1 participant each.

[b] After randomization to the ecopipam group, 1 participant discontinued because of an AE of abdominal pain with onset prior to study start.

[c] AE of suicidal ideation began during the open-label period, with subsequent progression to a serious AE after randomization to the placebo group.

[d] ≥5.0% of Ecopipam-treated participants.

[e] Tremor and dystonia were reported in 1 participant each during the open-label period; both instances were determined to be unrelated to ecopipam by a masked clinical adjudication committee.

The most frequently reported AEs:
- somnolence (n = 24 [11.1%])
- anxiety (n = 21 [9.7%])
- headache (n = 21 [9.7%])
- insomnia (n = 19 [8.8%])
- tic (n = 17 [7.9%])
- fatigue (n = 14 [6.5%])

No clinically meaningful impact on
- weight
- metabolic parameters
- psychiatric scale measures

No drug-induced movement disorders

Podcasts

NEWS

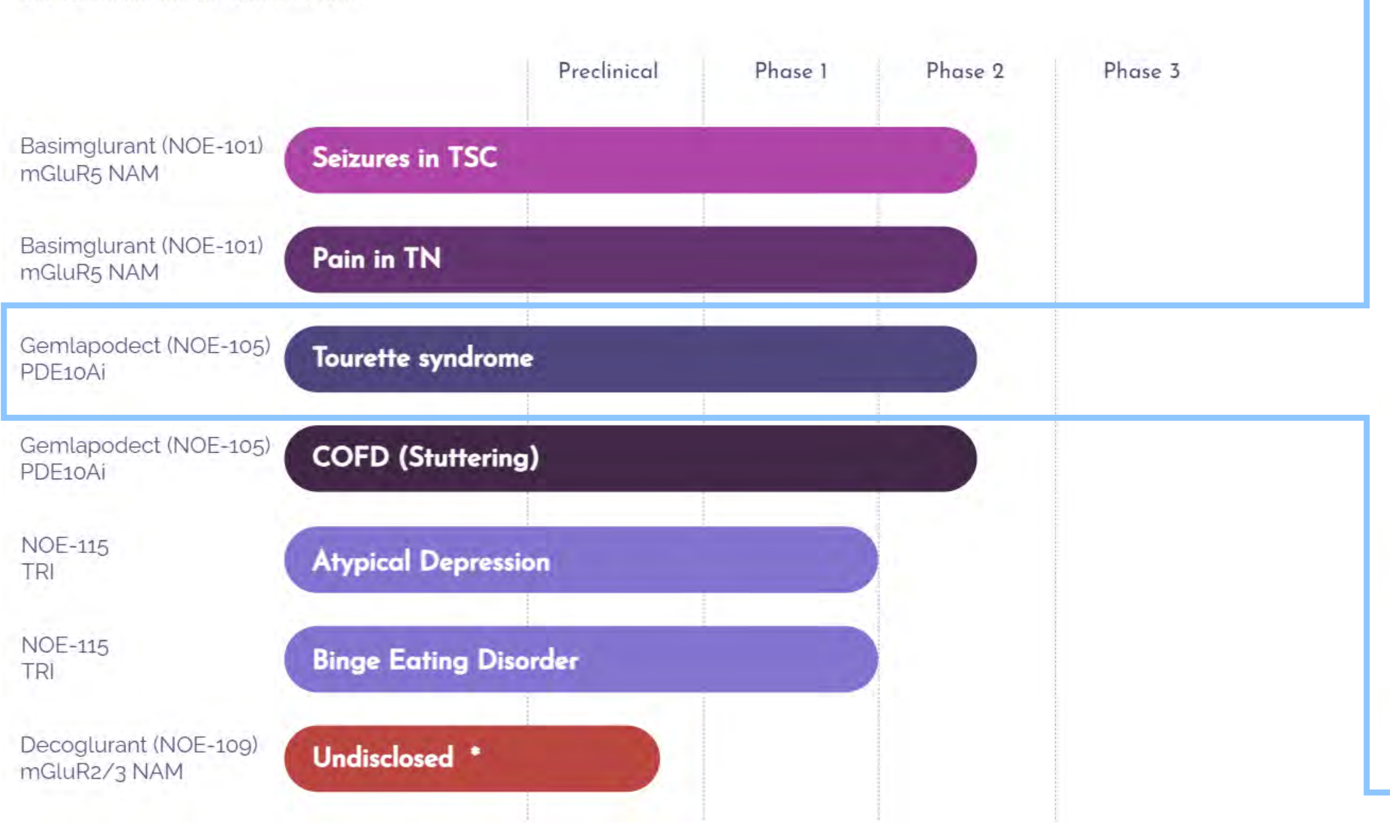
Results from Phase III Study of Ecopipam for Tourette Syndrome

Key findings, limitations and clinical perspectives on the important phase III study of Ecopipam for TS; taking a closer look with Dr Don Gilbert

For our November episode, and following his talk at the Athens 2025 Conference, we speak with Dr Gilbert about Ecopipam, a promising new treatment for Tourette syndrome that has recently completed phase 3 clinical trial.

The discussion explores the need for better therapeutic options in the current treatment landscape of Tourette syndrome and traces Ecopipam's journey from early animal studies through its clinical development programme. Dr Gilbert explains its mechanism of action and reviews the preclinical evidence that first suggested its potential benefit for Tourette syndrome. The conversation covers the drug's initial exploration in other clinical applications, before pivoting to its development specifically for TS.
The episode provides an in-depth look at three earlier clinical trials that demonstrated Ecopipam's benefit in individuals with TS, examining both their promising results and inherent limitations. Dr Gilbert then walks through the comprehensive methodology of the phase 3 study, explaining the rationale behind the chosen study design and the involvement of 99 sites worldwide that enrolled 216 subjects in the open-label phase.
Key efficacy findings are discussed for both paediatric and adult populations, including specific reductions in YGTSS Total Tic Severity scores. The conversation addresses the critical safety profile, examining psychological, metabolic, and extrapyramidal side effects, with particular attention to concerns regarding suicidality signals observed in the trial data.
He also shares insights on Ecopipam's effects on psychiatric comorbidities commonly associated with Tourette syndrome, acknowledges the study's limitations, and discusses available data from the extension phase.
The episode concludes with perspectives on anticipated regulatory timelines in the United States and Europe, along with Dr Gilbert's thoughts on where Ecopipam might fit in the treatment algorithm and any additional considerations for clinicians and patients.

Dr Gilbert is Professor of Neurology at Cincinnati Children's Hospital Medical Center, where he established the Movement Disorders and Tourette Clinics in 1998 and conducts translational research and clinical trials.



Gemlapodect (NOE-105)

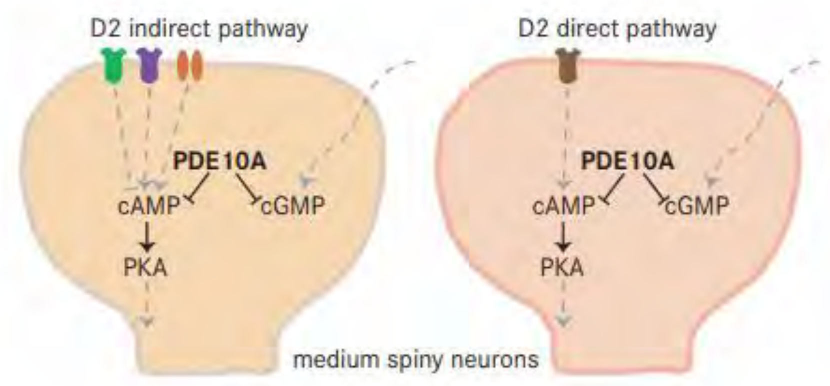
PDE10A inhibitor

For the management of Tourette Syndrome (TS) tics

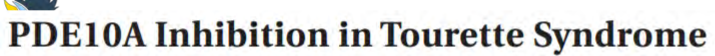
Clinical stage: Phase 2a

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.



NeurologyLive.com
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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

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

Active, not 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 2026-03-09

Study Start (Actual)

2024-09-10

Primary Completion (Estimated)

2026-06

Study Completion (Estimated)

2026-06

Enrollment (Actual)

164

Study Type

Interventional

Phase

Phase 2

ESSTS

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

J Neuropsychiatry Clin Neurosci 33:4, Fall 2021

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

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.

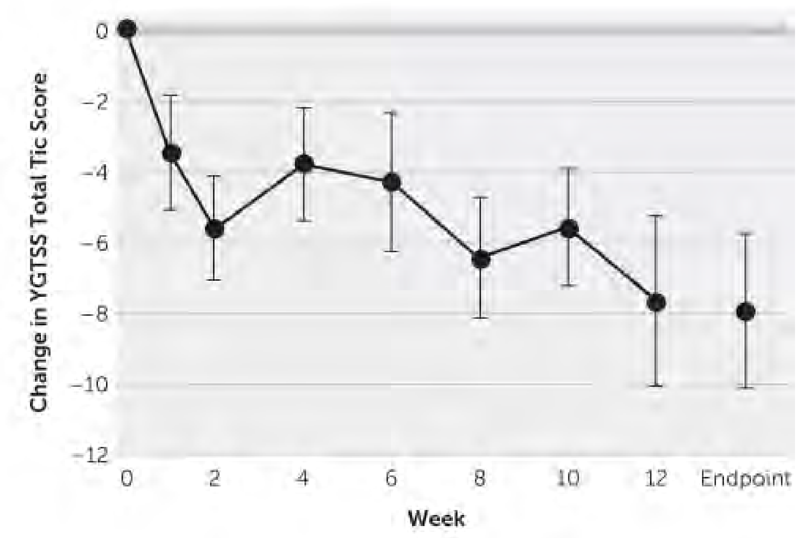
Methods: A 12-week uncontrolled trial of THX-110 (maximum daily Δ^9-THC dose, 10 mg, and a constant 800-mg dose of PEA) in 16 adults with Tourette's syndrome was conducted. The primary outcome was improvement on the Yale Global Tic Severity Scale (YGTSS) total tic score. Secondary outcomes included measures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

Treatment of Tics: Summary

- 1. Choice: antipsychotics
  - Aripiprazole
- 2. Choice:
  - Other antipsychotics: risperidone, tiaprid (in children)
  - Comorbid ADHD: clonidine
  - Cannabis-based medicine
  - Botulinum toxin
- Future: possibly ecopipam