D J Med Sci 2024;10(3):149-158
doi: 10.5606/fng.btd.2024.164

Review

Therapeutic approaches in Tourette syndrome: From behavioral therapy to deep brain stimulation

Hatice Gündüz[1], Oytun Erbaş[2]

[1]*Biruni Üniversitesi, Pharmacy, Istanbul, Türkiye*
[2]*Institute of Experimental Medicine, Gebze-Kocaeli, Türkiye*

ABSTRACT

Tourette syndrome (TS) is a neurodevelopmental disorder that begins in childhood and peaks during adolescence. It is characterized by motor and phonic tics occurring before the age of 18. The condition may arise from various environmental and genetic factors. Patients undergo a comprehensive evaluation, followed by the selection of an appropriate treatment method, such as behavioral therapy, pharmacotherapy, or deep brain stimulation (DBS). Given the side effects of medications and the complications associated with DBS, more reliable studies are needed. Comprehensive genomic studies and advanced imaging techniques are expected to elucidate the etiology of the disease. This review discusses the symptoms of TS, the factors contributing to its development, and the available treatment approaches.

Keywords: Deep brain stimulation, tic disorders, Tourette syndrome, treatment.

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by symptoms including multiple motor tics and at least one phonic tic lasting for more than one year. According to the Diagnostic and Statistical Manual of Mental Disorders in the United States, a diagnosis of TS requires the onset of tics before the age of 18, as well as a history of at least one year involving a minimum of two motor tics and one vocal tic.[1] The disorder typically begins around the ages of 6-7, peaks during adolescence, and is more commonly observed in males. Tics are often preceded by a sensory stimulus described as an "increasing inner tension".[2,3]

Approximately 60-75% of patients with TS also have attention-deficit hyperactivity disorder (ADHD), while 27% may present with obsessive-compulsive disorder (OCD).[4] Approximately 86% of patients with TS meet the diagnostic criteria for one or more comorbid psychiatric disorders.[5] Some studies have found enhanced abilities in inhibitory control, procedural memory, and habit formation in individuals with TS.[6-9]

Individuals with TS may exhibit co-occurring characteristics such as autism traits, learning difficulties, anxiety, depression, phobias, irritability, impulsivity, anger, aggression, sleep difficulties, oppositional defiant behavior, conduct and personality disorders, or a tendency for substance use.[10] Studies have found that individuals with TS experience attachment anxiety in their relationships.[11] The anger and aggression commonly observed in individuals with TS are thought to be caused by comorbid ADHD.[12]

The etiology of tics should not be directly influenced by factors such as cocaine use or other medical conditions like Huntington's disease.[13] Tics should occur several times a day, nearly every day, with no tic-free phase lasting longer than three consecutive months.

Received: January 06, 2025
Accepted: January 14, 2025
Published online: January 24, 2025

Correspondence: Hatice Gündüz.
E-mail: hatice.gunduz268@gmail.com

Cite this article as:
Gündüz H, Erbaş O. Therapeutic approaches in Tourette syndrome: From behavioral therapy to deep brain stimulation. D J Med Sci 2024;10(3):149-158. doi: 10.5606/fng.btd.2024.164.

Tics typically decrease during adolescence and completely resolve in one-third of patients.[14] According to a follow-up study, up to 23% of patients may experience persistent tics, and in some cases, severe tics may persist into adulthood.[15]

FACTORS CAUSING TOURETTE SYNDROME

Tourette syndrome is a complex genetic disorder characterized by highly variable phenomenology, pathophysiology, and etiology. Various genetic and environmental factors are associated with TS. Environmental factors such as prenatal (maternal smoking, low birth weight), perinatal (perinatal hypoxia, preterm birth), and postnatal (certain infections and psychological stress) influences may be linked to the disorder.[16]

Genetic factors play a significant role in the etiology of TS. Tourette syndrome is highly polygenic, and it has been confirmed that various genetic variants are widely distributed throughout the genome.[17] Copy number variations, which involve polymorphisms in the number of gene copies due to chromosomal deletions or duplications, are considered another important source of TS mutations. The CNTN6, NRXN1, SLITRK1, and HDC are risk genes that affect TS by approximately 1%.[18] A specific genetic marker for this disease cannot be identified.

According to the findings of a study indicating that TS is a neurodevelopmental disorder, children with TS exhibit more advanced brain functional connectivity, while adults with TS show less brain functional connectivity. This difference may be due to variations in cell and axon pruning, which can be influenced by both environmental and genetic factors.[19] In individuals with TS, the distribution of cerebellin-1 and cerebellin-2 is different.[20] The dysregulation of microRNA networks also plays a role in the development of many neurodevelopmental disorders, including TS.[21]

Advancements in electrophysiology and neuroimaging have revealed a decrease in the volume of the frontal cortex and a reduction in long-range connectivity between the frontal lobe and other regions of the brain. Tics may be a product of dysfunction in inhibitory functions within the sensorimotor cortex-basal ganglia network.[22]

In the onset of tics, increased activity has been reported in the primary motor cortex and cerebellum.[23,24] Studies in pediatric TS patients have highlighted abnormal white matter in the orbitofrontal cortex.[25,26] In children with tic disorders and comorbid OCD, reduced volumes of the caudate nucleus and putamen have been found.[27,28]

In individuals with TS, abnormal levels of activity are observed in the insular cortex and neural networks involved in tic production, including motor cortex regions and the putamen, compared to healthy controls. A functional connectivity magnetic resonance imaging study has shown that increased activity in the precuneus is positively correlated with the intensity of the provoking impulses. Using electroencephalography, the left precuneus has been identified as a central hub for increased connectivity during tic suppression.[29]

Studies suggest that individuals with TS exhibit increased low-frequency power (1-10 Hz) activity in the central thalamus, which may be related to tics. Other studies have also supported the presence of low-frequency activity in the anterior globus pallidus of TS patients.[30]

Tourette syndrome is associated with dysfunction in the cortico-striatal-thalamo-cortical brain circuits, which play a role in the selection of movements, as well as impaired inhibitory (GABAergic) signaling in the striatum and cortical motor areas. It is also linked to heightened excitability in the limbic and sensorimotor regions of the brain, which may contribute to the onset of tics.[31]

The pathophysiological hypothesis is based on dopaminergic dysfunction in the cortico-striatal-thalamo-cortical circuits.[32] The pathophysiology of TS is associated with impaired migration of cholinergic interneurons to the striatum, disrupted dopaminergic transmission, and, in rare monogenic forms, loss-of-function single nucleotide polymorphisms in the SLITRK1 gene.[33]

Dysfunctions in the dopamine system may be due to length polymorphisms in the gene locus of the dopamine receptor subtype D2. Polysomnographic and voluntary eye movement assessments have suggested a link between the hypofunction of nigrostriatal dopamine neurons and receptor supersensitivity. Serotonergic receptors and the SLC6A4 transporter genes are also implicated.[34]

The activities of dopamine and serotonin (5-HT) neurons, which play a critical role from late infancy to early childhood, are fundamental components in the pathophysiology of TS. The cause of simple tics involves dopamine neurons innervating the primary affected basal ganglia-thalamo-cortical circuits, as well as 5-HT neurons innervating the striatum, which regulates posture, tone, and non-motor functions. Complex tics, on the other hand, are triggered by dysfunctional cortical areas after the functional maturation of the basal ganglia's ascending pathways.[35] If the activity of 5-HT neurons is preserved or improved, the tics may remain pronounced, but the comorbidities of TS could be milder.

Several studies have observed that individuals with TS have greater activation of the hypothalamic-pituitary-adrenal axis and produce higher amounts of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol.[36] Immunoglobulin synthesis may be impaired in individuals with TS.[37] In TS, dysfunctional histamine receptor-mediated signaling predisposes to tic formation. Later genetic studies have provided further evidence that irregular histaminergic signaling, its variations, and single nucleotide polymorphisms play a causal role in TS through excessive transmission in humans.[38]

A rare mutation in the gene encoding histidine has been identified in a two-generation pedigree in association with TS.[39] In individuals with TS and a healthy control group, when measuring plasma levels of multiple cytokines, increased basal levels of tumor necrosis factor-alpha and interleukin-12 were observed.[40]

The gamma-aminobutyric acid receptors and hyperpolarization-activated cyclic nucleotide-gated channels identified in the brain transcriptome of individuals with TS provide evidence that the TS phenotype may be affected by dysfunction in inhibitory circuits, as previously suggested.[41]

A study found that individuals with TS or tic disorders are more likely to be diagnosed with a streptococcal infection in the year preceding the onset of tics, suggesting that streptococcal infections may trigger tic behaviors.[42]

TREATMENT OF TOURETTE SYNDROME

According to the European Society for the Study of Tourette Syndrome in 2011, the patient is primarily assessed, and psychological interventions are applied. If treatment is not effective, pharmacological treatment is provided. In severe cases, deep brain stimulation (DBS) is performed. The Yale Global Tic Severity Scale (YGTSS) is the most commonly used rating scale for tic assessment in both clinical practice and research. The questionnaire asks individuals to rate the severity, number, frequency, intensity, complexity, and intervention related to their tics. The impairment scale rates the impact of these tics on daily life. A higher score corresponds to more severe tics. A study conducted in 2021 showed that the YGTSS is specific for tics.[43]

Effective treatments for children with mild to moderate tics include specific behavioral techniques such as exposure and response prevention, habit reversal therapy, and Comprehensive Behavioral Intervention for Tics (CBIT).[44]

Non-pharmacological treatments primarily include psychoeducation and supportive therapy for tics, CBIT, acupuncture, and other similar approaches.[45] The 2011 European clinical guidelines recommended these treatments.

Psychoeducation involves teaching about a condition's symptoms, causes, prognosis, management, and daily experiences in a current and clear manner. A review indicates that psychoeducation has a positive impact on increasing beneficial behaviors in individuals with TS.[46]

Behavioral training

Habit reversal therapy consists of training to increase awareness of tics and triggering

impulses, along with competitive response training that involves identifying and applying physical responses that prevent the expression of tics.

Current tics are listed according to their level of severity. Once the patient has learned to reliably use a competing response to prevent a tic, the treatment focus shifts to the next most severe tic. The CBIT, an expanded version of habit reversal therapy, includes therapeutic strategies such as relaxation training, situation management, and interventions based on functional analyses to address factors influencing tic expression.[47]

In another form of exposure and response prevention therapy, all tics are addressed simultaneously. Initially, the patient is trained to suppress their tics, with suppression durations measured using a stopwatch, and the patient is motivated through multiple trials. In the next phase, the patient is exposed to triggers, and they are encouraged to practice in various situations, optimizing the process.[48]

Third-wave interventions, as part of behavioral therapies, include concepts such as metacognitive training, mindfulness, and psychological flexibility. These approaches suggest that accepting symptoms, rather than attempting to control them, may reduce their negative effects.[49]

Pharmacological treatment

First-line treatments include clonidine, guanfacine, haloperidol, fluphenazine, pimozide, risperidone, and tetrabenazine.[50]

Guanfacine is commonly used in TS patients, as well as in children with ADHD and tics who cannot take stimulant medications, to stop unrelated motor and vocal tics. Central α-adrenergic agents, such as clonidine or guanfacine, are typically the first line of treatment. Since they can cause hypotension, it is important to monitor blood pressure. There is also a risk of rebound hypertension if the medication is suddenly discontinued. The potential for the medication to cause underlying issues, such as ADHD and susceptibility to addiction, should also be considered.[51]

Antipsychotics in small doses, such as risperidone, aripiprazole, amisulpride, or haloperidol, can help control tics. When prescribing second-generation antipsychotics like risperidone or aripiprazole, weight gain and metabolic effects should be monitored. When considering medication for tics, the effects on comorbid disorders should also be taken into account. Aripiprazole may be preferred in patients with TS who also have OCD, anxiety, or major depressive disorder. Significant reductions in tics have been observed in a group of patients treated with aripiprazole and guanfacine.[52] Risperidone is effective in treating tics in TS and is considered safe for short-term management.[53]

These medications are used less frequently today due to the risk of extrapyramidal syndrome. Long-term use of dopamine receptor antagonists can lead to extrapyramidal symptoms, such as dystonia, akathisia, and tardive dyskinesia. Dopamine receptor antagonists can cause significant metabolic disturbances, leading to weight gain, insulin resistance, and generally increasing long-term cardiovascular risk. In a randomized study involving 10 weeks of use, it was observed that these medications increased body mass index compared to placebo.[54] A wide range of side effects have been reported, including sedation, dizziness, drowsiness, muscle tremors, dyskinesia, other extrapyramidal symptoms, and metabolic syndrome.

Tetrabenazine, a vesicular monoamine transporter type 2 inhibitor that depletes dopamine from synaptic terminals, can also be used for TS; however, it has side effects such as nausea, drug-induced parkinsonism, and depression.[55]

Olanzapine has been observed to be more effective than pimozide in reducing the severity of tics.[56] Among other antipsychotics, olanzapine has significant activity at 5-HT receptors, more so than dopamine receptors, and therefore produces fewer extrapyramidal symptoms.

Less commonly used treatments include anticonvulsants, benzodiazepines, and cannabinoids. topiramate, an anticonvulsant also used as a mood stabilizer, is better tolerated and more effective for children with TS when compared to haloperidol and tiapride. Studies

have shown that topiramate is effective in reducing tics and has been found to decrease behavioral and emotional issues.[57] Topiramate has side effects, including kidney stones, weight loss, and issues with speech and cognition.

Benzodiazepines like clonazepam may be effective for mild TS. A study has proven that botulinum toxin injections are an effective and safe treatment for TS tics.[58]

In several small-scale studies with limited evidence, a reduction in motor and vocal tics has been observed. For example, two patients using Sativex® showed significant improvement in both motor and vocal tics.[59]

Jing-an, an oral liquid, is a Chinese herbal formula used in the treatment of TS; however, its mechanism of action is not well understood.[60] In a clinical study with deutetrabenazine, no significant difference was observed compared to the placebo group.[61]

One of the candidate drug targets, the Chinese medicinal herb Semen Ziziphi Spinosae, is commonly used as a sedative and tranquilizer in the treatment of insomnia, anxiety, and other neuropsychiatric disorders. Studies have shown that Semen Ziziphi Spinosae exhibits neuroprotective activities through its antioxidant and anti-inflammatory effects.[62]

Gastrodia elata, a Chinese herb, contains the active compound gastrodin (Gas), which has a wide range of beneficial effects on conditions such as headaches, migraines, dizziness, infantile convulsions, and tetany. In a study focusing on the dopamine and 5-HT systems to assess the anti-tic role of Gas in a TS rat model, it was observed that Gas could potentially exhibit therapeutic effects in TS.[63]

Qiangzhi decoction is a traditional Chinese medicine that can alleviate the symptoms of TS. It may serve as a potential treatment for comorbid TS, but further validation of its neurotransmitter and immunomodulatory effects is needed.[64]

Fecal microbiota transplantation and other treatments

Another study observed in case examples of children with TS is fecal microbiota transplantation. Wang's study[65] suggested that there may be a disruption in the gut microbiota of patients with TS, and that improvement in the gut microbiota could correlate with improvement in tic symptoms. In patients with TS, the relative abundance of *Firmicutes* in their feces is lower compared to healthy children, while the relative abundance of Proteobacteria is higher.

After eight weeks of fecal microbiota transplantation, the gut microbial composition, particularly *Bacteroides coprocola*, has significantly changed.[66]

In Xi et al.'s study,[67] children with TS exhibited different levels of *Ruminococcus* and *Bacteroides plebeius* compared to children with chronic tic disorder. In a TS mouse model, weekly fecal microbiota transplantation resulted in a significant increase in the abundance of *Turicibacteraceae* and *Ruminococcaceae*. The group treated with tiapride and probiotics showed significant improvement in their YGTSS scores.

Promising formulations include the intranasal use of lurasidone. Instead of antagonizing the 5-HT2A receptor or partially agonizing the 5-HT1A receptor, the antagonism of the 5-HT7 receptor may play a significant role in lurasidone's effects on cognitive function when used to treat atypical antipsychotic-resistant cognitive disorders.[68]

Drugs administered via the nasal route can bypass the blood-brain barrier, leading to higher bioavailability.[69] Continuous use of nasal formulations can cause irritation of the nasal mucosa, potentially negatively impacting patient adherence and the safety of therapeutic interventions.[70] One of the side effects of lurasidone, which requires attention along with the downregulation of the 5-HT7 receptor, is sleep disturbance.[71] Advanced technologies are required in intranasal formulations to enhance therapeutic efficacy and maintain stability.

Phosphodiesterase 10A inhibitors are continuing to be researched for a wide range of indications (schizophrenia, TS, childhood-onset fluency disorder, L-dopa-induced dyskinesia in Parkinson's disease). Unlike other medications,

they are associated with a reduced risk of metabolic syndrome.[72]

Clonidine transdermal patch can safely and effectively reduce tic symptoms in TS patients with ADHD and may potentially be beneficial in controlling ADHD symptoms. The site of action for clonidine is the locus coeruleus. The plasma concentration of the transdermal patch does not reach a peak, and continuous use over a week is required to achieve maximum efficacy and fewer side effects.[73]

Deep brain stimulation

Some patients do not respond to pharmacological treatments, including α2 adrenergic agonists, dopamine receptor antagonists, benzodiazepines, antiepileptic drugs, and botulinum toxin injections. This may lead to self-harming behaviors (e.g., cervical myelopathy, bone fractures, retinal detachment) and potentially result in temporary or permanent disabilities for some patients with refractory TS. In these cases, both DBS and ablative neurosurgical procedures can be used to manage resistant symptoms.

Deep brain stimulation is an invasive treatment reserved for severe cases that do not respond to other therapeutic approaches.[74] In DBS, an electrode is implanted in the brain to provide electrical activity, which helps restore brain functions. In TS, multiple brain regions are targeted during DBS to suppress tics. Deep brain stimulation for the treatment of TS should be conducted in specialized centers by a trained multidisciplinary team consisting of a psychiatrist, psychologist, and/or neurologist. According to the Tourette Association of America database, prior to DBS, the patient's co-occurring psychiatric conditions must be stabilized, and the patient should not have had active suicidal or homicidal thoughts for the past six months.[75] Deep brain stimulation is considered a last resort due to challenges in patient selection, ethical concerns in pediatric patients, and the fact that it does not yield the same results for every patient.

Deep brain stimulation involves the surgical implantation of stimulation electrodes into various motor regions of the brain's cortico-basal ganglia-thalamo-cortical circuit, including the subthalamic nucleus, globus pallidus internus (GPi), and ventral intermediate nucleus.

The first surgical treatment involving thalamotomy in the ventromedial-perifascicular complex and ventro-oralis internus nucleus resulted in a 70-100% reduction in tics.[76]

Deep brain stimulation of the centromedian and parafascicular nucleus complex has been reported to reduce the severity of motor tics and comorbid psychiatric symptoms in patients with TS. Reported side effects include temporary blurred vision, dysarthria, recurrent tension-type headaches, and a single seizure-like episode. In one study, DBS of the medial thalamic region resulted in an average of 50% improvement in overall tic severity after a 6-month follow-up.[77]

According to imaging studies, the globus pallidus, an element of the basal ganglia-thalamo-cortical circuit implicated in the pathophysiology of TS, has been identified as a promising DBS target for managing severe and refractory TS.[78] A multicenter study in TS patients with medial GPi DBS reported improvements in tic severity, comorbid OCD, anxiety, depression, and quality of life. Posteroventral GPi DBS stabilized comorbid OCD symptoms in one patient.[79]

Several case studies have suggested other targets for TS treatment, such as the anterior limb of the internal capsule, the nucleus accumbens, or a combination of multiple targets. However, DBS in these regions may lead to emotional side effects. Some studies have reported clinical improvements in TS patients when DBS is targeted at the junction of multiple adjacent thalamic nuclei.[79] An alternative target includes the Forel's field H1, through which projections from the GPi to the thalamus pass. This area has been found to be an effective and well-tolerated alternative target in two resistant TS cases.[80]

As a result, no significant difference was observed among the targets investigated in DBS. Ablation and DBS are interventions that block the abnormal signaling in the basal ganglia-thalamocortical network in TS patients. Studies investigating the use of repetitive transcranial magnetic stimulation (rTMS) as a treatment

for TS have typically targeted the primary motor cortex or the supplementary motor area. Activation of the supplementary motor area through neurofeedback may be effective in improving tic symptoms.[81]

Studies have shown that in patients with TS, the structure and function of the parietal cortex are abnormal. According to these studies, low-frequency bilateral rTMS targeting the parietal cortex may regulate its function and enhance inhibition. Improvements in neural plasticity have been observed following rTMS interventions.[82]

Rhythmic mu-band (10 Hz) frequency has been found to be sufficient to significantly reduce both the frequency and intensity of tics in individuals with TS. This frequency can be delivered to patients through wearable devices that they can easily use in their daily lives.[83]

In the treatment of TS, individualized assessment methods and multidisciplinary care are essential. Treatment stages such as behavioral therapy, pharmacological interventions, and DBS should be carefully evaluated. Lesion network mapping, a new neuroimaging technique that maps lesions to brain networks rather than anatomical locations, has been proposed to address this challenge. More comprehensive imaging studies are needed for TS. Increasing large-scale collaborative studies can provide insights into genetic factors and treatment development. New techniques, such as ex vivo organoids derived from induced pluripotent stem cells, may clarify pathophysiology. Genome-wide association studies will be helpful in further elucidating the underlying genetic etiology of the disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control/supervision, critical review: O.E.; Data collection and/or processing, analysis and/or interpretation, literature review, writing the article, references and fundings: H.C.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. American Psychiatric Association . Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Cavanna AE, Nani A. Tourette syndrome and consciousness of action. Tremor Other Hyperkinet Mov (N Y) 2013;3:tre-03-181-4368-1. doi: 10.7916/D8PV6J33.
3. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry 1993;150:98–102. doi: 10.1176/ajp.150.1.98.
4. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: Selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol 2000;42:436–47. doi: 10.1017/s0012162200000839.
5. Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 2015;72:325-33. doi: 10.1001/jamapsychiatry.2014.2650.
6. Kalsi N, Tambelli R, Aceto P, Lai C. Are motor skills and motor inhibitions impaired in Tourette syndrome? A review. J Exp Neurosci 2015;9:57–65. doi: 10.4137/JEN.S25095.
7. Jackson GM, Draper A, Dyke K, Pépés SE, Jackson SR. Inhibition, disinhibition, and the control of action in Tourette syndrome. Trends Cogn Sci 2015;19:655–65. doi: 10.1016/j.tics.2015.08.006.
8. Takács Á, Kóbor A, Chezan J, Éltető N, Tárnok Z, Nemeth D, et al. Is procedural memory enhanced in Tourette syndrome? Evidence from a sequence learning task. Cortex 2018;100:84–94. doi: 10.1016/j.cortex.2017.08.037.
9. Delorme C, Salvador A, Valabrègue R, Roze E, Palminteri S, Vidailhet M, et al. Enhanced habit formation in Gilles de la Tourette syndrome. Brain 2016;139:605–15. doi: 10.1093/brain/awv307.
10. Eapen V, Črnčec R, McPherson S, Snedden C. Tic disorders and learning disability: Clinical characteristics, cognitive performance and comorbidity. Australas J Spec Educ 2013;37:162–72. doi: 10.1017/jse.2013.2.
11. Dehning S, Burger MB, Krause D, Jobst A, Yundina E, Müller N, et al. Tourette syndrome is associated with insecure attachment and higher aggression. Int J Neurosci 2014;125:521–5. doi: 10.3109/00207454.2014.951040.
12. Freeman RD. Tourette Tourette Syndrome International Database Consortium Tic disorders and ADHD: Answers from a world-wide clinical dataset on Tourette syndrome. Eur Child Adolesc Psychiatry 2007;16:15–23. doi: 10.1007/s00787-007-1003-7.

13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
14. Kurlan R., Shprecher D. Uncommon Causes of Movement Disorders. In: Galvez-Jiménez N, Tuite P, editors. Tourette syndrome and other tic disorders. Cambridge: Cambridge University Press; 2011. p. 180-184.
15. Groth C, Mol Debes N, Rask CU, Lange T, Skov L. Course of Tourette syndrome and comorbidities in a large prospective clinical study. J Am Acad Child Adolesc Psychiatry 2017;56:304-12. doi: 10.1016/j.jaac.2017.01.010.
16. Ludolph AG, Roessner V, Münchau A, Müller-Vahl K. Tourette syndrome and other tic disorders in childhood, adolescence and adulthood. Dtsch Arztebl Int 2012;109:821-288. doi: 10.3238/arztebl.2012.0821.
17. Davis LK, Yu D, Keenan CL, Gamazon ER, Konkashbaev AI, Derks EM, et al. Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture. PLoS Genet 2013;9:e1003864. doi: 10.1371/journal.pgen.1003864.
18. Huang AY, Yu D, Davis LK, Sul JH, Tsetsos F, Ramensky V, et al. Rare copy number variants in NRXN1 and CNTN6 increase risk for Tourette syndrome. Neuron 2017;94:1101–11.e7. doi: 10.1016/j.neuron.2017.06.010.
19. Marín O. Developmental timing and critical windows for the treatment of psychiatric disorders. Nat Med 2016;22:1229-38. doi: 10.1038/nm.4225.
20. Seigneur E, Wang J, Dai J, Polepalli J, Südhof TC. Cerebellin-2 regulates a serotonergic dorsal raphe circuit that controls compulsive behaviors. Mol Psychiatry 2021;26:7509-21. doi: 10.1038/s41380-021-01187-x.
21. Perkins DO, Jeffries CD, Jarskog LF, Thomson JM, Woods K, Newman MA, et al. microRNA expression in the prefrontal cortex of individuals with schizophrenia and schizoaffective disorder. Genome Biol 2007;8:R27. doi: 10.1186/gb-2007-8-2-r27.
22. Kataoka Y, Kalanithi PS, Grantz H, Schwartz ML, Saper C, Leckman JF, et al. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. J Comp Neurol 2010;518:277-91. doi: 10.1002/cne.22206.
23. Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, et al. Neural correlates of tic generation in Tourette syndrome: An event-related functional MRI study. Brain 2006;129:2029–37. doi: 10.1093/brain/awl050.
24. Neuner I, Werner CJ, Arrubla J, Stöcker T, Ehlen C, Wegener HP, et al. Imaging the where and when of tic generation and resting state networks in adult Tourette patients. Front Hum Neurosci 2014;8:362. doi: 10.3389/fnhum.2014.00362.
25. Müller-Vahl KR, Kaufmann J, Grosskreutz J, Dengler R, Emrich HM, Peschel T. Prefrontal and anterior cingulate cortex abnormalities in Tourette syndrome: Evidence from voxel-based morphometry and magnetization transfer imaging. BMC Neurosci 2009;10:47. doi: 10.1186/1471-2202-10-47.
26. Plessen KJ, Bansal R, Peterson BS. Imaging evidence for anatomical disturbances and neuroplastic compensation in persons with Tourette syndrome. J Psychosom Res 2009;67:559–73. doi: 10.1016/j.jpsychores.2009.07.005.
27. Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. Neurology 2005;65:1253–8. doi: 10.1212/01.wnl.0000180957.98702.69.
28. Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, et al. Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. Arch Gen Psychiatry 2003;60:415-24. doi: 10.1001/archpsyc.60.4.415.
29. Morand-Beaulieu S, Wu J, Mayes LC, Leckman JF, Crowley MJ, Sukhodolsky DG. Increased alpha-band connectivity during tic suppression in children with Tourette syndrome revealed by source electroencephalography analyses. Biol Psychiatry Cogn Neurosci Neuroimaging 2023;8:241-250.
30. Neumann WJ, Huebl J, Brücke C, Lofredi R, Horn A, Saryyeva A, et al. Pallidal and thalamic neural oscillatory patterns in Tourette's syndrome. Ann Neurol 2018;84:505-14. doi: 10.1002/ana.25311.
31. Albin RL, Mink JW. Recent advances in Tourette syndrome research. Trends Neurosci 2006;29:175–82. doi: 10.1016/j.tins.2006.01.001.
32. Ünal D, Akdemir D. Tourette sendromunun nörobiyolojisi. Türk Psikiyatri Dergisi 2016;27:275-85. doi: 10.5080/u13640.
33. O'Rourke JA, Scharf JM, Yu D, Pauls DL. The genetics of Tourette syndrome: A review. J Psychosom Res 2009;67:533-45. doi: 10.1016/j.jpsychores.2009.06.006.
34. Lin WD, Tsai FJ, Chou IC. Current understanding of the genetics of Tourette syndrome. Biomed J 2022;45:271-9. doi: 10.1016/j.bj.2022.01.008.
35. Segawa M. Neurophysiology of Tourette's syndrome: Pathophysiological considerations. Brain Dev 2003;25:S62–9. doi: 10.1016/s0387-7604(03)90011-8.
36. Caligiore D, Mannella F, Arbib MA, Baldassarre G. Dysfunctions of the basal ganglia-cerebellar-thalamo-cortical system produce motor tics in Tourette syndrome. PLoS Comput Biol 2017;13:e1005395. doi: 10.1371/journal.pcbi.1005395.
37. Bos-Veneman NG, Olieman R, Tobiasova Z, Hoekstra PJ, Katsovich L, Bothwell AL, et al. Altered immunoglobulin profiles in children with Tourette syndrome. Brain Behav Immun 2011;25:532–8. doi: 10.1016/j.bbi.2010.12.003.

38. Fernandez TV, Sanders SJ, Yurkiewicz IR, Ercan-Sencicek AG, Kim YS, Fishman DO, et al. Rare copy number variants in Tourette syndrome disrupt genes in histaminergic pathways and overlap with autism. Biol Psychiatry 2012;71:392-402. doi: 10.1016/j.biopsych.2011.09.034.
39. Ercan-Sencicek AG, Stillman AA, Ghosh AK, Bilguvar K, O'Roak BJ, Mason CE, et al. L-histidine decarboxylase and Tourette's syndrome. N Engl J Med 2010;362:1901-8. doi: 10.1056/NEJMoa0907006.
40. Leckman JF, Katsovich L, Kawikova I, Lin H, Zhang H, Krönig H, et al. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. Biol Psychiatry 2005;57:667–73. doi: 10.1016/j.biopsych.2004.12.004.
41. Rapanelli M, Frick LR, Pittenger C. The role of interneurons in autism and Tourette syndrome. Trends Neurosci 2017;40:397–407. doi: 10.1016/j.tins.2017.05.004.
42. Leslie DL, Kozma L, Martin A, Landeros A, Katsovich L, King RA, et al. Neuropsychiatric disorders associated with streptococcal infection: A case-control study among privately insured children. J Am Acad Child Adolesc Psychiatry 2008;47:1166-72. doi: 10.1097/CHI.0b013e3181825a3d.
43. Haas M, Jakubovski E, Fremer C, Dietrich A, Hoekstra PJ, Jäger B, et al. Yale Global Tic Severity Scale (YGTSS): Psychometric quality of the gold standard for tic assessment based on the large-scale EMTICS study. Front Psychiatry 2021;12:626459. doi: 10.3389/fpsyt.2021.626459.
44. Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, et al. Behavior therapy for children with Tourette disorder: A randomized controlled trial. JAMA 2010;303:1929-37. doi: 10.1001/jama.2010.607.
45. Geng JZ, Xu JY, Wang XG, Liu YQ, Cui YN, Li XM. Acupuncture: A new method to treat tic disorders in children. Traditional Medicine Research 2022;7:16. doi:10.53388/TMR20220127259.
46. Nussey C, Pistrang N, Murphy T. How does psychoeducation help? A review of the effects of providing information about Tourette syndrome and attention-deficit/hyperactivity disorder. Child Care Health Dev 2013;39:617–27. doi: 10.1111/cch.12039.
47. Woods DW, Piacentini JC, Chang SW, Deckersbach T, Ginsburg GS, Peterson AL, et al. Managing Tourette syndrome: a behavioral intervention for children and adults: therapist guide. Treatments that work. New York: Oxford University Press; 2008.
48. Hoogduin K, Verdellen C, Cath D. Exposure and response prevention in the treatment of Gilles de la Tourette's syndrome: Four case studies. Clin Psychol Psychother 1997;4:125–35.
49. Hayes SC, Strosahl K, Wilson KG. Acceptance and commitment therapy: an experiential approach to behavior change. New York: Guilford Press; 1999.
50. Kurlan R. Tourette's syndrome. N Engl J Med 2010;363:2332–8. doi: 10.1056/NEJMcp1007805.
51. Olden GS. Gilles de la Tourette's syndrome following methylphenidate administration. Dev Med Child Neurol 1974;16:76–8. doi: 10.1111/j.1469-8749.1974.tb02715.x.
52. George T, Emig M, Chand P, Hendry H. Successful treatment of Tourette syndrome with a combination of guanfacine and aripiprazole: A case series. Cureus 2023;15:e39573. doi: 10.7759/cureus.39573.
53. Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology 2003;60:1130-5. doi: 10.1212/01.wnl.0000055434.39968.67.
54. Yoo HK, Joung YS, Lee JS, Song DH, Lee YS, Kim JW, et al. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. J Clin Psychiatry 2013;74:e772-80. doi: 10.4088/JCP.12m08189.
55. Porta M, Sassi M, Cavallazzi M, Fornari M, Brambilla A, Servello D. Tourette's syndrome and role of tetrabenazine: Review and personal experience. Clin Drug Investig 2008;28:443-59. doi: 10.2165/00044011-200828070-00006.
56. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: Pharmacological treatment. Eur Child Adolesc Psychiatry 2011;20:173-96. doi: 10.1007/s00787-011-0163-7.
57. Kuo SH, Jimenez-Shahed J. Topiramate in treatment of Tourette syndrome. Clin Neuropharmacol 2010;33:32-4. doi: 10.1097/WNF.0b013e3181c295c1.
58. Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol 2000;57:1190-3. doi: 10.1001/archneur.57.8.1190.
59. Mouhamed Y, Vishnyakov A, Qorri B, Sambi M, Frank SS, Nowierski C, et al. Therapeutic potential of medicinal marijuana: An educational primer for health care professionals. Drug Healthc Patient Saf 2018;10:45-66. doi: 10.2147/DHPS.S158592.
60. Xi L, Ji X, Ji W, Yang Y, Zhang Y, Long H. Jing-an oral liquid alleviates Tourette syndrome via the NMDAR/MAPK/CREB pathway in vivo and in vitro. Pharm Biol 2022;60:1790-800. doi: 10.1080/13880209.2022.2116056.
61. Mannix KC, Li D, Beker Y. Teva announces registration trials of deutetrabenazine in pediatric patients with Tourette syndrome did not meet the primary endpoint. TEVA; 2020. Available at: https://www.businesswire.com/news/home/20200219005903/en/
62. Liu Z, Zhao X, Liu B, Liu AJ, Li H, Mao X, et al. Jujuboside A, a neuroprotective agent from semen Ziziphi Spinosae ameliorates behavioral disorders of the dementia mouse model induced by Aβ 1-42. Eur J Pharmacol 2014;738:206-13. doi: 10.1016/j.ejphar.2014.05.041.

63. Huang JH, Wang GL. Studies on some pharmacological effects of gastrodia injection and gastrodin. 1985;7:399-402.
64. Jiang Y, Zhan T, Wang M, Duan Y, Wu X, Song A, et al. Integrated UPLC-MS, network pharmacology, and intestinal flora analysis to determine the treatment effect of Qiangzhi decoction on comorbid Tourette syndrome and RRTI. Ann Transl Med 2023;11:299. doi: 10.21037/atm-23-936.
65. Wang Z. Effect of pediatric massage combined with acupuncture on gut microbiota structure of children with Tourette Syndrome. [MA Thesis]. Mongolia: Inner Mongolia Medical University; 2021.
66. Zhao HJ, Luo X, Shi YC, Li JF, Pan F, Ren RR, et al. The efficacy of fecal microbiota transplantation for children with Tourette syndrome: A preliminary study. Front Psychiatry 2020;11:554441. doi: 10.3389/fpsyt.2020.554441.
67. Xi W, Gao X, Zhao H, Luo X, Li J, Tan X, et al. Depicting the composition of gut microbiota in children with tic disorders: An exploratory study. J Child Psychol Psychiatry 2021;62:1246–54. doi: 10.1111/jcpp.13409.
68. Okubo R, Hasegawa T, Fukuyama K, Shiroyama T, Okada M. Current limitations and candidate potential of 5-HT7 receptor antagonism in psychiatric pharmacotherapy. Front Psychiatry 2021;12:623684. doi: 10.3389/fpsyt.2021.623684.
69. Costa C, Moreira JN, Amaral MH, Sousa Lobo JM, Silva AC. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. J Control Release 2019;295:187-200. doi: 10.1016/j.jconrel.2018.12.049.
70. Bharat B, Sharma K, Yadav V. Intranasal drug delivery system: A review. Research Journal of Science and Technology 2024;16:51-8. doi: 10.52711/2349-2988.2024.00009
71. Okubo R, Hasegawa T, Fukuyama K, Shiroyama T, Okada M. Current limitations and candidate potential of 5-HT7 receptor antagonism in psychiatric pharmacotherapy. Front Psychiatry 2021;12:623684. doi: 10.3389/fpsyt.2021.623684.
72. Marshall RD, Menniti FS, Tepper MA. A novel PDE10A inhibitor for Tourette syndrome and other movement disorders. Cells 2024;13:1230. doi: 10.3390/cells13141230.
73. Chen Y, Ke Z, Ouyang Y, Han Y, Liang D, Gao X, et al. Clonidine patch for Tourette syndrome with attention-deficit/hyperactivity disorder. Psychiatry Investig 2024;21:387-95. doi: 10.30773/pi.2023.0262.
74. Xu W, Zhang C, Deeb W, Patel B, Wu Y, Voon V, et al. Deep brain stimulation for Tourette's syndrome. Transl Neurodegener 2020;9:4. doi: 10.1186/s40035-020-0183-7.
75. Schrock LE, Mink JW, Woods DW, Porta M, Servello D, Visser-Vandewalle V, et al. Tourette syndrome deep brain stimulation: A review and updated recommendations. Mov Disord 2015;30:448-71. doi: 10.1002/mds.26094.
76. Rickards H, Wood C, Cavanna AE. Hassler and Dieckmann's seminal paper on stereotactic thalamotomy for Gilles de la Tourette syndrome: Translation and critical reappraisal. Mov Disord 2008;23:1966–72. doi: 10.1002/mds.22238.
77. Dowd RS, Pourfar M, Mogilner AY. Deep brain stimulation for Tourette syndrome: A single-center series. J Neurosurg 2018;128:596–604. doi: 10.3171/2016.10.JNS161573.
78. Ji GJ, Liao W, Yu Y, Miao HH, Feng YX, Wang K, et al. Globus pallidus interna in Tourette syndrome: Decreased local activity and disrupted functional connectivity. Front Neuroanat 2016;10:93. doi: 10.3389/fnana.2016.00093.
79. Huys D, Bartsch C, Koester P, Lenartz D, Maarouf M, Daumann J, et al. Motor improvement and emotional stabilization in patients with Tourette syndrome after deep brain stimulation of the ventral anterior and ventrolateral motor part of the thalamus. Biol Psychiatry 2016;79:392-401. doi: 10.1016/j.biopsych.2014.05.014.
80. Neudorfer C, El Majdoub F, Hunsche S, Richter K, Sturm V, Maarouf M. Deep brain stimulation of the H fields of Forel alleviates tics in Tourette syndrome. Front Hum Neurosci 2017;11:308. doi: 10.3389/fnhum.2017.00308.
81. Sukhodolsky DG, Walsh C, Koller WN, Eilbott J, Rance M, Fulbright RK, et al. Randomized, sham-controlled trial of real-time functional magnetic resonance imaging neurofeedback for tics in adolescents with Tourette syndrome. Biol Psychiatry 2020;87:1063-70. doi: 10.1016/j.biopsych.2019.07.035.
82. Black KJ, Black ER, Greene DJ, Schlaggar BL. Provisional tic disorder: What to tell parents when their child first starts ticcing. F1000Res 2016;5:696. doi: 10.12688/f1000research.8428.1.
83. Morera Maiquez B, Sigurdsson HP, Dyke K, Clarke E, McGrath P, Pasche M, et al. Entraining movement-related brain oscillations to suppress tics in Tourette syndrome. Curr Biol 2020;30:2334-42.e3. doi: 10.1016/j.cub.2020.04.044.