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Tourette's syndrome: III. Treatment Portfolio and Prognosis

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Abstract

In this Article, I will detail the treatment portfolio for the Tourette's syndrome, including: Pharmacology; orphan, repurposed, off-label, and compassionate use medicines; complementary and alternative treatments; and brain neurostimulation that includes deep brain simulation, repetitive transcranial magnetic stimulation, transcranial electrotherapy, and continuous theta-burst stimulation. I will elaborate on the various available drug categories with emphasis on their applicability, safety, efficacy, results, side effects, adverse events, and even the levels of confidence in the results of the undergirding clinical trials used to formulate the corresponding treatment recommendations. I will give more particular attention to those drugs that are currently FDA-approved and reconstruct their respective Facts Sheets. Such considerations will be particularized for children, adults, pregnant women, co-occurring medical conditions, and the respective clinical practice guielines. Additionally, I dwell at length on the various brain neurostimulation approaches tested so far, highlighting the individual stimulated brain regions, the technologies employed, our (unfortunately limited) experience with them, the corresponding clinical practice guidelines, and the treatment benefits, risks, and complications. I will finally outline the prognosis following such procedures.

Abbreviations

AAN: American Academy of Neurology; ADHD: Attention-Deficit Hyperactivity Disorder; ATMP: Advanced Therapy Medicinal Products; BNS: Brain NeuroStimulation; CBD: Cannabidiol; CBIT: Comprehensive Behavioral Intervention for Tics; CETS: Cranial ElectroTherapy Stimulation; CHMP: (EMA's) Committee for Medicinal Products for Human Use; CI: Confidence Interval; COMP: (Europe's) Committee for Orphan Medicinal Products; cTBS: continuous TBS: CUM: Compassionate Use Program; CUS: Compassionate Use Medicines; DBS: Deep Brain Stimulation; DSM: (AAN's) Diagnostic & Statistical

Manual of Mental Diseases; EC: European Commission; ECG: Electrocardiogram; ECROM: European Community Register of Orphan Medicinal Products; EMA: European Medicines Agency; EU: European Union; FDA: (U.S.) Food and Drug Administration; GABA: Gamma-AminoButyric Acid; HTA: Health Technology Assessment; IPG: Implantable Pulse Generator; IRB: Institutional Review Board; ITS-DBS-PDR: International Tourette's Syndrome DBS Public Database and Registry; LEC: Local Ethics Committee; LMA: Lateral Motor Area; MGP: Medial Globus Pallidus; MNS: Median Nerve Stimulation; OCD: Obsessive-Compulsive Disorder; OLM: Off-Label Medicines; OM: Orphan medicines; OMPR: (EU) Orphan Medicinal Products Regulation; PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections; QOL: Quality Of Life; RCT: Randomized Clinical Trial; RPM: RePurposed Medicines; rTMS: repetitive TMS; SMA: Supplementary Motor Area; SMD: Standard Mean Deviation; SORM: Sensory Over-Responsive Manifestation; SSRI: Selective Serotonin Re-uptake Inhibitors; TBS: Theta-burst Stimulation; TCE: Transcranial Electrotherapy; THC: Tetrahydrocannabinol; TMS: Transcranial Magnetic Simulation; TS: Tourette's Syndrome; tVNS: transcutaneous VNS: VNS: Vagus Nerve Stimulation; WHO: World Health Organization.

Keywords

Brain neurostimulation; Cranial electrotherapy stimulation; Deep brain stimulation; Orphan, repurposed, off-label, and compassionate use medicines; Transcranial magnetic stimulation.

Introduction

In addition to approaches for the management of symptoms (elaborated upon on Article II in this series), the treatment portfolio for TS includes: Pharmacology; orphan, repurposed, off-label, and compassionate use medicines; complementary and alternative treatments; and brain neurostimulation (BNS) that includes deep brain simulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial electrotherapy (TCE), and continuous theta burst stimulation (cTBS), as will be presented in the next sections.

Pharmacological

Each person with TS is an individual who will require an individualized treatment plan. It is important to note that not everyone with TS will need medical treatment and medical treatment needs can vary over time. While there is no cure for TS, there are a number of medical treatments (including the non-medicine behavioral treatments discussed in Article II) that can be effective at reducing tics or helping to manage co-occurring conditions. There is no one medication that is helpful to all people with TS, nor does any medication completely eliminate symptoms.

If tic symptoms are mild and do not cause impairment, there may be no need for treatment. If, however, they interfere with daily functioning, there are effective medications and other treatments. Sometimes, the associated disorders are more impairing than the tics themselves and may be treated instead as this may improve tic severity. Some medications may have or cause side effects and should be carefully managed by the attending physician or healthcare provider. Children with tics typically present when their tics are most severe but, because the condition waxes and wanes, medication is not started immediately or changed often. Tics may subside with education, reassurance, and a supportive environment. When medication is used, the goal is not to eliminate symptoms. Instead, the lowest dose that manages symptoms without adverse effects is used because such effects may be more disturbing than the symptoms being treated with medication.

As indicated in Article II, it is common for people with TS to have other conditions, particularly ADHD and

OCD. Based on these symptoms, people with additional conditions will require different treatments. Sometimes, treating these other conditions can help reduce tics. To develop the right treatment plan, people with tics, their parents and healthcare providers can work together and also include other family members, teachers, childcare providers, coaches, and therapists. Taking advantage of all the resources available will help guide success.

Treatment goal

The goal of treatment with medications is to reduce tics to a point that they are no longer causing distress to the patient or interfere with function. The currently available medications are not cures and the tics may not completely resolve. Tics still wax and wane in frequency and severity, and fluctuations will continue to occur whether or not medication is used.

Sometimes, what may seem to be an initial response to a medication may simply have been a coincidence if tics were beginning to wane at the same time the medication was introduced. All treatments have potential side effects or risks and a doctor will weigh what is known about the potential benefit of a therapy versus the potential risks for the individual patient. Once a medication plan is decided, a doctor will monitor the patient's response and any adverse reactions. It is important to note that medications may take some time to work. It is not unusual to have to go through some trial-and- error to determine which medication (or combination of medications) works best for the patient as each patient will respond differently.

Medicating TS

Medications can be used to reduce severe or disruptive tics that might have led to problems in the past with family and friends, other students, or co-workers. They can also be used to reduce symptoms of related conditions, such as ADHD or OCD although they might not be helpful for everyone. Unfortunately, they do not eliminate tics completely. However, they can help some people with TS in their everyday life. There is no one medication that is best for all people. Most medications prescribed for TS have not been approved by the (U.S.) Food and Drug Administration (FDA) for treating tics (they have been repurposed from other applications).

Medications affect each person differently. One person might do well with one medication, but not another. When deciding the best treatment, a doctor might try different medications and doses, and it may take time to find the treatment plan that works best. The doctor will want to find the medication and dose that have the best results and the fewest side effects. Doctors often start with small doses and slowly increase the dose as needed.

Medications can have long-term and short-term adverse effects. As with all medications, those used to treat tics can have side effects, which can include weight gain, stiff muscles, tiredness, restlessness, and social withdrawal. The side effects need to be considered carefully when deciding whether or not to use any medication to treat tics as, in some cases, the side effects can be worse than the tics. For some people with TS, two common reasons for not using medications are their unpleasant side effects and their failure to work as well as expected.

For a full summary on the available evidence on different medications for TS, the American Academy of Neurology (AAN) has issued in 2019 its "Tourette Treatment Guidelines".

Types of Medications

Below are some of the types of medications used for tic suppression (see Table 1):

• **Anti-hypertensives:** Examples are Clonidine, Guanfacine, Haloperidol, and Pimozide. These alpha-adrenergic agonists (dopamine blockers) are marketed to control high blood pressure. They may be used to treat psychotic and non-psychotic disorders. They have

variable efficacy but a lower side effect profile than the neuroleptics. They are typically tried first in children but can also help with ADHD symptoms. For most children, both the benefits and the side effects are modest. However, there is less evidence that they are effective for adults. They are the most consistently useful medications to suppress tics.

• **Antipsychotics:** These are the most effective class of medication to treat tics. They work by decreasing dopamine functioning. Side effects can include weight gain, diabetes, and increased breast tissue. If they are used for a long period of time, they can cause tardive dyskinesia (or abnormal and involuntary body movements).

• **Antidepressants/ anti-anxiety medicines:** Examples are Clomipramine, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline. Specifically the selective serotonin re-uptake inhibitors (SSRI) can help some people control symptoms of depression, OCD, and anxiety.

• Anti-seizure medicines.

• **Neuroleptics:** Examples are Risperidone and Aripiprazole. They are employed when antihypertensives are not effective, and are generally tried first for adults. Because of lower side effects, Aripiprazole is preferred over other antipsychotics.

• **Stimulants:** Example,s are Methylphenidate and Dextroamphetamine. They can lessen ADHD symptoms in people with TS without causing tics to become more severe.

• **Other medications:** A variety of other medications can help such as:

◦ Medicines for other movement disorders.

◦ Nicotine.

◦ Cannabidiol (CBD) and other cannabis-derived agents.

Haloperidol (Haldol), Pimozide (Orap), and Aripiprazole (Abilify) are currently the only medications approved by the FDA to treat tics. However, physicians may start with "off-label" use (not FDA-approved specifically for the treatment of tics) of Guanfacine or Clonidine, both of which are alpha-adrenergic agonist medications that are approved for use in the treatment of high blood pressure. These medications have been found to be moderately effective in reducing tics and to be better tolerated. The most effective medication for tics is Haloperidol, but it has a higher risk of side effects. Methylphenidate can be used to treat co-occurring ADHD in combination with Clonidine.

During pregnancy

A quarter of women report that their tics increase before menstruation; however, studies have not shown consistent evidence of a change in frequency or severity of tics related to pregnancy or hormonal levels. Overall, symptoms in women respond better to *Haloperidol* than they do for men. One report found that *Haloperidol* could be used during pregnancy, to minimize the side effects in the mother, including low blood pressure, and anticholinergic effects, although it may cross the placenta.

Most women find they can withdraw from medication during pregnancy without much trouble. When needed, medications are used at the lowest doses possible. During pregnancy, neuroleptic medications are avoided when possible because of the risk of pregnancy complications. When needed, *Olanzapine*, Risperidone and Quetiapine are most often used as they have not been shown to cause fetal abnormalities.

If severe tics might interfere with administration of local anesthesia, other anesthesia options are considered. Neuroleptics in low doses may not affect the breast-fed infant, but most medications are avoided. *Clonidine* and *Amphetamines* may be present in breast milk.

Medications for co-occurring conditions

Co-occurring conditions, such as ADHD and OCD, often require medication, which can improve the quality of life in patients with TS. It is not unusual for the treatment of these conditions to result in a reduction of tics. Inattention, impulsivity, and hyperactivity are common symptoms seen in patients with ADHD; they can be an obstacle for school-aged children. Stimulant medications, such as *Methylphenidate* can be effective in children who have TS and ADHD. Other non-stimulant medications, such as *Guanfacine, Clonidine, Atomoxetine* may also be beneficial. Selective serotonin re-uptake inhibitors (SSRIs), such as *Fluoxetine, Sertraline, and Fluvoxamine* are effective in youth and adults with anxiety/OCD. Side effects are generally tolerable (Table 1).

Medication	**Indication**	**Action & Side effects**
Amphetamines	o Psychoanaleptic o Hallucinogenic o Empathogenic	o May be present in breast milk
Aripiprazole (neuroleptic)	o Tried first in adults (additional trials on-going)	o Lower side effects than anti-hypertensives and preferred over them o Not used during pregnancy because of risk of complications
Clonidine (anti-hypertensive)	o Typically for children o Helps with ADHD	o Variable efficacy in children, less for adults o Lower side effect profile than the neuroleptics o May be present in breast milk
Guanfacine (anti-hypertensive)	o Typically for children o Helps with ADHD	o Variable efficacy in children, less for adults o Lower side effect profile than the neuroleptics
Haloperidol	o Against tics	o Most effective o Higher risk of side effects o More responsive in women
Methylphenidate	o Against ADHD when co-occurring with tics o Can be used in combination with *Clonidine*	o Nervousness o Trouble sleeping o Loss of appetite o Weight loss o Dizziness o Nausea o Vomiting o Headache
Olanzapine (neuroleptic)	o Used during pregnancy	o Not shown to cause fetal abnormalities o May not affect the breast-fed infant
Quetiapine (neuroleptic)	o Used during pregnancy	o Not shown to cause fetal abnormalities o May not affect the breast-fed infant
Selective serotonin re-uptake inhibitors	o To manage anxiety and OCD	o Diarrhea o Nausea o Vomiting o Dizziness o Trouble sleeping

Table 1: Medication classes for TS and co-occurring conditions

In Europe, practitioners have shifted from Risperidone to mostly using Aripiprazole as a first-line therapy followed by Risperidone, Clonidine, Guanfacine (children) and Topiramate (adults), respectively. Remarkably, although being the only officially licensed drug for tic treatment in most European countries, Haloperidol is no longer used there as a preferred drug. Facts Sheets for the FDA-approved TS drugs are provided in the Appendix.

Confidence levels in the several medicines

For the purpose of ascertaining the level of confidence in their respective benefits, researchers have conducted systematic reviews of all available medicines and their applications to TS and co-occurring conditions. The scientific question posed was: "In children and adults with TS or a chronic tic disorder, which medical, behavioral, and neurostimulation interventions, compared with placebo or other active interventions, improve tic severity?" The results are summarized in Tables 2 below for several confidence levels in the evidence for tic treatments (high, moderate, low, very low, and insufficient) compared to placebo in reducing tic severity.

Treatment	Confidence level
CBIT (Comprehensive Behavioral Intervention for Tics)	**High** SMD 0.56 (95%), CI 0.31–0.82, High confidence, 2 Class I studies

SMD= Standard Mean Deviation; CI=Confidence Interval

Table 2(a): High confidence level in the evidence for tic treatments

Treatment	Confidence level
Aripiprazole	**Moderate** SMD 0.64 (95%), CI 0.31–0.97 1 Class I study and 1 Class II study (children only)
Clonidine	SMD 0.45 (95%) CI 0.13–0.77 1 Class I study and 2 Class II studies
Haloperidol	SMD 0.59 (95%) CI 0.11–1.06 2 Class II studies
Onabotulinumtoxin-A injections	SMD 1.27 (95%) CI 0.51–2.03 1 Class II study; confidence in evidence upgraded due to magnitude of effect
Risperidone	SMD 0.79 (95%) CI 0.31–1.27 2 Class II studies
Tiapride	SMD 0.62 (95%) CI 0.36–0.88 1 Class I study (children only)
5-Ling granule	SMD 0.55 (95%) CI 0.33–0.76 1 Class I study (children only)
Ningdong granules (as formulated by Zhao)	SMD 0.97 (95%) CI 0.45–1.49 1 Class II study; confidence in evidence upgraded due to magnitude of effect (children only)

Table 2(b1): Moderate confidence level in the evidence for tic treatments

Treatment	Confidence level
Clonidine plus Methylphenidate,	**Moderate** SMD 0.72 (95%) CI 0.22–1.22 1 Class I study (children only)
Desipramine Now rarely used in children after several case reports of associated sudden deaths	SMD 1.13 (95%) CI 0.47–1.79 1 Class II study; confidence in evidence upgraded due to magnitude of effect (children only)
Methylphenidate	SMD 0.61 (95%) CI 0.13–1.10 1 Class I study (children only)

Table 2(b2): Moderate confidence level in the evidence for tic plus ADHD treatments

Treatment	Confidence level
Guanfacine	**Low** SMD 0.45 (95%) CI 0.03–0.87 1 Class I study and 2 Class II studies, confidence in evidence downgraded due to imprecision (children only)
Metoclopramide	SMD 1.14 (95%) CI 0.33–1.95 1 Class II study (children only)
Pimozide	SMD 0.66 (95%) CI 0.06–1.25 3 Class II studies, confidence in evidence downgraded due to imprecision
Tetrahydrocannabinol	SMD 0.62 (95%) CI 0.01–1.22 1 Class II study and 1 Class III study (adults only)
Topiramate	SMD 0.91 (95%) CI 0.11–1.71 1 Class II study
Ziprasidone	SMD 1.14 (95%) CI 0.32–1.97 1 Class II study (children only)

Table 2(c1): Low confidence level in the evidence for tic treatments

Treatment	Confidence level
Atomoxetine	**Low** Does not worsen tics relative to placebo 1 Class II study (children only).

Table 2(c2): Low confidence level in the evidence for tic plus ADHD treatments

Treatment	Confidence level
Baclofen	**Very low** SMD 0.55 (95%) CI −0.39 to 1.49 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Deprenyl	SMD 0.47 (95%) CI −0.05 to 0.99) 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Flutamide	1 Class I study (adults only)
IV immunoglobulin	SMD 0.50 (95%) CI −0.24 to 1.24 1 Class II study; confidence in evidence downgraded due to imprecision
Levetiracetam	SMD 0.22 (95%) CI −0.38 to 0.82 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Mecamylamine	1 Class II study (children only)

N-acetylcysteine	SMD 0.45 (95%) CI −0.27 to 1.17 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Nicotine	SMD 0.38 (95%) CI −0.14 to 0.90 1 Class III study (children only)
Nicotine patch added to Haloperidol	SMD 0.71 (95%) CI 0.17–1.25 1 Class III study (children only)
Omega-3 fatty acids	SMD 0.69 (95%) CI 0.00–1.39) 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Ondansetron	SMD 0.53 (95%) CI −0.20 to 1.25 1 Class III study
Pramipexole	SMD 0.00 (95%) CI −0.53 to 0.53 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Riluzole	SMD 0.17 (95%) CI −0.91 to 1.25) 1 Class I study; confidence in evidence downgraded due to imprecision (children only)
d-Serine	SMD −0.04 (95%) CI −1.13 to 1.05 1 Class I study; confidence in evidence downgraded due to imprecision (children only)
Ningdong granules (as formulated by Wang)	1 Class II study (children only)

Table 2(d): Very low confidence level in the evidence for tic treatments

Treatment	Confidence level
Baclofen	**Very low** SMD 0.55 (95%) CI −0.39 to 1.49 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Deprenyl	SMD 0.47 (95%) CI −0.05 to 0.99) 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Flutamide	1 Class I study (adults only)
IV immunoglobulin	SMD 0.50 (95%) CI −0.24 to 1.24 1 Class II study; confidence in evidence downgraded due to imprecision
Levetiracetam	SMD 0.22 (95%) CI −0.38 to 0.82 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Mecamylamine	1 Class II study (children only)
N-acetylcysteine	SMD 0.45 (95%) CI −0.27 to 1.17 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Nicotine	SMD 0.38 (95%) CI −0.14 to 0.90 1 Class III study (children only)
Nicotine patch added to Haloperidol	SMD 0.71 (95%) CI 0.17–1.25 1 Class III study (children only)
Omega-3 fatty acids	SMD 0.69 (95%) CI 0.00–1.39) 1 Class II study; confidence in evidence downgraded due to imprecision (children only)
Ondansetron	SMD 0.53 (95%) CI −0.20 to 1.25 1 Class III study
Pramipexole	SMD 0.00 (95%) CI −0.53 to 0.53 1 Class II study; confidence in evidence downgraded due to imprecision (children only)

Riluzole	SMD 0.17 (95%) CI −0.91 to 1.25) 1 Class I study; confidence in evidence downgraded due to imprecision (children only)
d-Serine	SMD −0.04 (95%) CI −1.13 to 1.05 1 Class I study; confidence in evidence downgraded due to imprecision (children only)
Ningdong granules (as formulated by Wang)	1 Class II study (children only)

Table 2(e): Insufficient confidence level in the evidence for tic treatments

Risks and harms

In children and adults with TS or a chronic tic disorder, what are the risks of harm, including weight gain, elevated prolactin levels, sedation, drug-induced movement disorders, hypotension, bradycardia, and electrocardiogram (ECG) changes with medical treatments compared with placebo or other active interventions? These are summarized in Table 3 for several medicines.

Risk or harm	Medicine
Weight, body mass, waist circumference: o Tics only: o Tics with ADHD:	 o Increase with: *Aripiprazole, Risperidone* o Decrease with: *Atomoxetine*
Elevated prolactin levels	*Haloperidol*, *Metoclopramide*, or *Pimozide*
Sedation, fatigue, and somnolence	*Aripiprazole*, *Clonidine*, *Guanfacine*, *Risperidone*, or *Tiapride*
Drug-induced movement disorders	o Extrapyramidal symptoms: *Haloperidol*, *Pimozide* o Higher Parkinsonism on Extrapyramidal Symptom Rating Scale (ESRCS): *Risperidone*
Blood pressure: Tics + ADHD	Increase in diastolic pressure: *Desipramine*
Heart rate: Tics + ADHD	Increase: *Atomoxetine, Desipramine*
ECG changes	Prolonged QT interval: *Pimozide*

Table 3: Risks and harms of tic treatments

In summary, in the above studies, there was high confidence that CBIT was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that *Aripiprazole, Clonidine, Haloperidol, Onabotulinum, Risperidone, Tiapride, toxinA injections, 5-ling granule, and Ningdong granules* were probably more likely than placebo to reduce tics. There was low confidence that *Guanfacine, Metoclopramide, Pimozide, Tetrahydrocannabinol, Topiramate, and Ziprasidone*, were possibly more likely than placebo to reduce tics. Evidence of harm associated with various treatments was also demonstrated, including weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on heart rate, blood pressure, and ECGs.

Clinical practice guidelines

The clinical practice guidelines for the treatment of tics that were separately published by the American Academy of

Neurology (AAN), the European Union (EU), and the World Health Organization (WHO) were reviewed in Article II in this series. They consisted of 13 categories of recommendations, the first seven of which were more appropriate in the case of symptoms management. They included counseling, psychoeducation, assessment and treatment of ADHD in children with tics, assessment and treatment of OCD in children with tics, other psychiatric co-morbidities, assessment of tic severity and treatment expectations, and behavioral treatments. The remaining 6 categories for pharmacological treatment and neurostimulation are presented below. They include alpha-adrenergic agonists, antipsychotic treatment, Botulinum toxin injections, Topiramate. Cannabis-based medications, and deep-brain stimulation (DBS) in the TS setting. They have been summarized in Tables 4-9, respectively. Again, in these recommendations, when the benefit-to-harm ratio is favorable for any given intervention, three recommendation designations are provided (A for 'must'; B for 'should'; and C for 'may'), each designation denoting the strength level of the said recommendation, A being relatively the strongest one and C the weakest one.

Recommendation #	Level	Physician's role
8a	B	Should counsel individuals with tics and co-morbid ADHD that α2- adrenergic agonists may provide benefit for both conditions
8b	B	Should prescribe α2-adrenergic agonists for the treatment of tics when the benefits of treatment outweigh the risks
8c	A	Must counsel patients regarding common side effects of α2- adrenergic agonists, including sedation
8d	A	Must monitor heart rate and blood pressure in patients with tics treated with α2-adrenergic agonists
8e	A	When prescribing *Guanfacine* extended release: Must monitor the QTc interval in patients with a history of cardiac conditions, taking other QT-prolonging agents, or with a family history of long QT syndrome
8f	A	When discontinuing α2-adrenergic agonists: Must gradually taper them to avoid rebound hypertension

Source: AAN Recommended TS Guidelines (2019)

Table 4: Alpha-agonists for the treatment of tics

Rationale: People with tics receiving Clonidine are probably alpha-agonists for the treatment of tics and are more likely to have reduced tic severity. People with tics receiving Guanfacine have possibly reduced tic severity. In children with tics and co-morbid ADHD, Clonidine and Guanfacine have demonstrated beneficial effects on both tics and ADHD symptoms. However, abrupt withdrawal of α2- adrenergic agonists may cause rebound hypertension.

Recommendation #	Level	Physician's role
9a	C	May prescribe antipsychotics when the benefits of treatment outweigh the risks
9b	A	Must counsel patients on the relative propensity of antipsychotics for extrapyramidal, hormonal, and metabolic adverse effects to inform decision-making on which antipsychotics should be prescribed
9c	A	Must prescribe the lowest effective dose to decrease the risk of adverse effects
9d	B	Should monitor for drug-induced movement disorders and for metabolic and hormonal adverse effects of antipsychotics, using evidence-based monitoring protocols
9e	A	Must perform electrocardiography and measure the QTc interval before and after starting *Pimozide* or *Ziprasidone*, or if antipsychotics are co-administered with other drugs that can prolong the QT interval
9f	B	When attempting to discontinue antipsychotics for tics: Should gradually taper medications over weeks to months to avoid withdrawal dyskinesias

Table 5: Antipsychotic treatment for tics

Rationale: *Haloperidol, Risperidone, Aripiprazole, and Tiapride are probably more likely to reduce tic severity whereas Pimozide, Ziprasidone,* and *Metoclopramide* are possibly more likely to reduce tic severity. While there is insufficient evidence to determine the relative efficacy of these drugs, it demonstrates a higher risk of drug-induced movement disorders with *Haloperidol*, *Pimozide*, and *Risperidone*, a higher risk of weight gain with *Risperidone* and *Aripiprazole*, a higher risk of somnolence with *Risperidone*, *Aripiprazole*, and *Tiapride*, a higher risk of QT prolongation with *Pimozide*, and a higher risk of elevated prolactin with *Haloperidol, Pimozide*, and *Metoclopramide*. There is a higher risk of drug-induced movement disorders (including tardive dyskinesia, drug-induced parkinsonism, akathisia, acute dystonia, and tardive dystonia), weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation antipsychotics across psychiatric and neurologic conditions. The long-term use of *Metoclopramide* is associated with tardive dyskinesia. The relative propensity for these adverse effects varies by agent and is often dose-dependent.

Recommendation #	Level	Physician's role
10a	C	May prescribe *Botulinum* toxin injections for the treatment of adolescents and adults with localized and bothersome simple motor tics when the benefits of treatment outweigh the risks
10b	C	May prescribe *Botulinum* toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks
10c	A	Must counsel individuals with tics that *Botulinum* toxin injections may cause weakness and hypophonia, and that all effects are temporary

Table 6: Botulinum toxin injections for tics

Rationale: Botulinum toxin injections with Onabotulinumtoxin-A can reduce tic severity in adolescents and adults, may also improve premonitory urges, and is associated with higher rates of weakness. Hypophonia is a common side effect in the laryngeal muscles for vocal tics. The effects last 12–16 weeks, after which treatment needs to be repeated.

Recommendation #	Level	Physician's role
10a	B	Should prescribe *Topiramate* for the treatment of tics when the benefits of treatment outweigh the risks
10b	A	Must counsel patients regarding common adverse effects of *Topiramate*, including cognitive and language problems, somnolence, weight loss, and an increased risk of renal stones

Table 7: Topiramate for the treatment of tics

Rationale: Topiramate can reduce tic severity. It may be a useful alternative for patients with mild but troublesome tics who are not obtaining a satisfactory response or experience adverse effects from other treatments.

Recommendation #	Level	Physician's role
12a	A	Must offer to direct patients to appropriate medical supervision when cannabis is used as self-medication for tics. Appropriate medical supervision would entail education and monitoring for efficacy and adverse effects

12b	C	May consider treatment with cannabis-based medication in otherwise treatment-resistant adults with clinically relevant tics
12c	C	May consider treatment with cannabis-based medication in adults with TS who already use cannabis efficiently as a self-medication in order to better control and improve quality of treatment
12d	A	Must prescribe the lowest effective dose to decrease the risk of adverse effects
12e	A	Must inform patients that medication may impair driving ability
12f	A	Must periodically re-evaluate the need for ongoing treatment

Table 8: Cannabis-based medications for the treatment of patients with TS

Rationale: Some patients with TS use cannabis as a self-medication for tics and co-morbidities. There is limited evidence that δ-9-tetrahydrocannabinol (THC) and Dronabinol can reduce tic severity in adults with TS. There is insufficient evidence to determine whether the efficacy of Nabiximols, Nabilone, and Cannabidiol (CBD), as well as different strains of medicinal cannabis—standardized for different levels of THC and CBD—are similar to THC. Cannabis-based medications are associated with increased risk of short-term adverse events, most commonly dizziness, dry mouth, and fatigue. Controlled treatment with cannabis-based medication may induce addiction to cannabinoids. Acute withdrawal of cannabinoids is generally safe and well-tolerated without significant adverse events. Cannabis-based medications should be avoided in children and adolescents due to the association between cannabis exposure in adolescence and potentially harmful cognitive and affective outcomes in adulthood. Cannabis-based medications should not be used in women who are pregnant or breastfeeding or in patients with psychosis. Prescription of, and access to, medical marijuana must abide by regional legislation on the use of medical marijuana.

Orphan, repurposed, off-label, and compassionate use medicines

Orphan, repurposed, off-label, and compassionate use medicines are employed for rare diseases. While it merely describes the European situation, similar descriptions apply to other countries and are not discussed here.

Orphan medicines (OM)

OM are intended for the diagnosis, prevention or treatment of rare diseases. They may also be pediatric medicines for the treatment of rare diseases or advanced therapies in children. These medicines were called "orphan" because under normal market conditions (i.e. in the absence of an orphan regulation), the pharmaceutical industry has little interest in developing and marketing products intended for only a small number of patients, when the high cost of bringing a medicinal product to market may not be recovered by the expected sales of the product. In Europe, the EU Orphan Medicinal Products Regulation (OMPR) (2000) brought into place a range of incentives aimed at encouraging the development of medicines for rare diseases. Since 1999, there have been over 2000 orphan designations and around 200 orphan medicines authorized for the markets.

Development and authorization of orphan medicines

In Europe, the sponsor (public or private) developing an orphan medicine can apply to the European Medicines Agency (EMA) for orphan designation. After full review, the EMA's Committee for Orphan Medicinal Products (COMP) issues an opinion recommending whether the orphan designation should be granted and the European Commission (EC) makes the final decision. Once designation is granted and the development has progressed, the sponsor must submit

to the EMA an application for marketing authorization for assessment through the centralized procedure. The benefit-to-risk ratio of the medicine (i.e. the balance between the efficacy and safety of the medicine) is assessed by EMA's Committee for Medicinal Products for Human Use (CHMP). The EMA's CHMP makes a recommendation on whether or not a medicine should be authorized for use in humans (i.e. whether a market authorization should be granted). Of note, designated orphan medicines are eligible for conditional marketing authorization.

In parallel, the COMP reviews the criteria for orphan designation in order to assess whether the orphan status still holds. Then, the EC makes the final decision on whether to authorize the medicine based on that recommendation and whether to maintain this orphan status or not. (Note: The EMA has an interactive tool setting out the development and authorization of medicines for human use.) The list of the latest marketing authorizations and orphan medicinal products designations can be viewed in the "European Community Register of Orphan Medicinal Products (ECROM)".

Once a medicine is authorized at the EU level, the process moves to the national European country level. The national competent authorities for pricing and reimbursement decide whether the medicine can be provided and how. In many cases, a Health Technology Assessment (HTA) body assesses whether the medicine is safe and cost effective in comparison to existing medicines available in that country and provides a recommendation on whether that medicine should be reimbursed by the national healthcare system. The ultimate goal is to have authorized medicines available, affordable, and accessible for rare disease patients.

Safety

Pharmacovigilance is the science and activities related to the detection and reporting of side effects of a medicine, together with measures to minimize these risks. It is exercised across Europe in order to ensure the integrity and safety of medicinal products.

Repurposed medicines (RPM)

A RPM is a medicine already approved for human use in a certain indication and for which researchers or clinicians identify new disease(s) that the medicine could treat (i.e. a new indication). Because the medicine is already in use, some data are already available, especially regarding its safety profile. Additional data have to be collected through a clinical study to confirm the efficacy of the medicine in the new patient population. However, the repurposing approach brings advantages for a rare disease as it saves money and time in that a new compound does not have to be found and developed anew.

Off-label medicines (OLM)

When doctors prescribe a medicine for a use different from what is authorized on the label, this is called "off label" use, for example, when the drug is prescribed for a different disease or when the dosage differs from the one stated on the label. Patients with rare diseases and their families are often familiar with this practice, or may not even realize that they are taking products that are prescribed "off-label".

Compassionate use medicines (CUM)

A CUM is a medicinal product not yet fully evaluated but prescribed to treat people with no other therapeutic options.

What is a compassionate use program (CUP)?

Running a CUP consists of making a medicinal product available for compassionate reasons to a group of patients (or sometimes individual patients on a case-by-case basis) with a chronically or seriously debilitating

disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. In Europe, the corresponding legislation states that the medicinal requested that the medicine in question be already authorized somewhere in the world. If the product has been or is currently being tested in a clinical trial for the disease under consideration, the patient's doctor can request a compassionate use authorization. Most EU Member States have a special scheme to dispense medicines on a compassionate basis. Many other European and North American countries have similar processes. These processes are more or less complex and time consuming.

What a compassionate use program is not

A CUP is not an experiment or a clinical trial: It is intended to treat the person. By definition, a compassionate use is a treatment, although not yet fully evaluated for patients who do not have other options. Other circumstances when a medicine is given should not be confused with compassionate use.

product concerned must either be the subject of an application for a marketing authorization or must be undergoing clinical trials. In other terms, it is not

In no case can the medicinal product given on a compassionate use be a placebo, nor a treatment or combination of treatments that the patient has had before, lacking efficacy or poorly tolerated. Even though it is not completely certain whether the treatment the patient receives on a compassionate use basis is useful, if there is no other option and there is the slightest chance that the product will be effective, the patient should benefit from it. A CUP cannot replace clinical trials. Again, it is not an experiment. It cannot conclude whether the product is safe and effective on a group of patients. A CUP can be organized in parallel to clinical trials, but it can only be authorized if clinical trials are already in progress, and recruitment in a CUP should not be an obstacle for the recruitment of patients in clinical trials (for example, if patients prefer to receive the medicine on a compassionate basis and not take the risk of receiving a placebo as might be the case in a clinical trial).

Medicine	Orphan	Repurposed	Off-label	Compassionate Use
Acetylcysteine N-		o Lung diseases		
***Aripiprazole**		o Schizophrenia		
Atomoxetine		o Used to treat ADHD) as part of a total treatment plan, including psychological, social, and other treatments	o ADHD	
Baclofen		o Spinal cord injury/disease	o MS	
Benzodiazepine		o Seizures		
Botulinum		o Eye disorders o Muscle stiffness/ spasms o Migraine o Sweating o Drooling		
Clonidine		o Anti-hypertensive (Central alpha agonist:		
Deprenyl				

Desipramine		o Depression		
Guanfacine		o Anti-hypertensive		
***Haloperidol**		o Schizophrenia o **Tourette**		
Levitiracetam				
Mecamylamine		o Anti-hypertensive		
Methylphenidate		o Narcolepsy	o ADHD	
Metoclopramide		o GI diseases o Heartburn o Diabetic gastroparesis		
Nicotine		o Anti-smoking		
Omega-3				
Ondansetran				
***Pimozide**		o **Tourette**		
Pramipexole			o Parkinson's o Restless leg syndrome	
Riluzole			o ALS	
Risperidone			o Schizophrenia oBipolar disorder o Autistic disorder	
SSRI		o Anti-depressant		
Serine D-		o Coffee extract		
Tetrabenazine			o Huntington's disease chorea	
THC				
Topiramate		o Anticonvulsant/ antiepileptic		
Ziprasidone			o Schizophrenia o Bipolar disorder	

ALS=Amyotrophic lateral sclerosis (Lou Gehrig's disease); MS=Multiple sclerosis; SSRI=Selective serotonin re-uptake inhibitors; THC=(Delta-9) Tetrahydrocannabinol

(*) Sole (U.S.) FDA-approved medicines for use in the U.S.A.

Table 9: Classification of medicines used for Tourette's syndrome among orphan, repurposed, off-label, or compassionate use

Complementary and Alternative Medicine (CAM)

CAM approaches, such as allergy testing and control, dietary modification, and neurofeedback have popular appeal, but they have no proven benefit in the management of TS.

Despite this lack of evidence, up to two-thirds of parents, caregivers, and individuals with TS use dietary approaches and alternative treatments and do not always inform their physicians.

There is low confidence that tics are reduced with Tetrahydrocannabinol (THC) and insufficient evidence for other cannabis-based medications in the treatment of TS.

A meta-analysis did not find any evidence of benefit of THC whereas other isolated studies have shown some efficacy and safety.

There is no good evidence supporting the use of acupuncture, intravenous immunoglobulin, or plasma exchange. Neither is there evidence supporting the use of antibiotics for the treatment of PANDAS (pediatric

autoimmune neuropsychiatric disorders associated with streptococcal infections). Table 10 summarizes these observations:

Treatment	Indication	Action & Side effects
Allergy testing and control	o TS management	o No proven benefit
Dietary modification	o TS management	o No proven benefit
Neurofeedback	o TS management	o No proven benefit
Tetrahydrocannabinol (THC) & other cannabis-based agents	o TS treatment	o Low confidence in benefit
Acupuncture	o TS treatment	o No good supporting evidence of benefit
Intravenous immunoglobulin	o TS treatment	o No supporting evidence of benefit
Plasma exchange	o TS treatment	o No supporting evidence of benefit
Antibiotics	o Autoimmune neuropsychiatric disorders associated with streptococcal infections	o No supporting evidence of benefit

Table 10: Lack of benefit evidence of complementary and alternative treatments

However, supportive therapy can help a person with TS better cope with the disorder and deal with secondary social and emotional problems.

Advanced therapy medicinal products (ATMP)

ATMPs are medicines for human use that are based on genes, tissues or cells. They are highly relevant for the treatment of rare diseases as they might, for example, target the genetic cause of a rare disease. Research to develop ATMPs for rare diseases creates a pool of knowledge that can be highly valuable for the development of medicinal products for more common diseases.

Other treatment forms available for rare diseases

Assistive technologies and digital devices, medical devices, physiotherapy, radiotherapy, and surgery may also be used in the treatment of rare diseases.

Brain Neurostimulation (BNS)

In rare cases, patients severely disabled by TS. may not improve using standard approaches. In these cases, surgery can be an option. Surgeries include, deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (TDCS). In this article, I will discuss the principle and application of these procedures. They are administered more frequently in adults and they remain investigational in children. They need to be investigated further and used only at centers with expertise in the procedures.

Deep Brain Stimulation (DBS)

At present time, DBS in TS is still in its infancy. Due to differing legal jurisdictions and treatment facilities in different countries, guidelines issued by regulatory or/and other organizations and professional societies should be understood as recommendations of experts to be used in adult, treatment resistant, and severely affected patients. Further, it is highly recommended to perform DBS in the context of controlled trials.

DBS

therapy is a surgical treatment which aims to reduce tics and seizures that could not be controlled with medication, and where surgery to treat their cause is not possible. It has become a valid option for individuals

with severe symptoms that do not respond to conventional therapy and management, although it is an experimental treatment. Selecting candidates who may benefit from DBS is challenging, and the appropriate lower age range for surgery is unclear. It is potentially useful in less than 3% of individuals. The ideal brain location to target has not yet been identified as of 2019. People with tics receiving active DBS of the globus pallidus are probably more likely than those receiving sham DBS of that brain region to have reduced tic severity.

With growing evidence for the safety of DBS and results suggesting earlier intervention may be beneficial, researchers further examined its use for targeting other brain areas.

Further innovations are emerging with advances in neuroscience and technology. For example, while traditional DBS delivers constant stimulation, newer adaptive devices can self-tune stimulation in response to certain features of a person's brain activity or behavior. For example, one such closed-loop device had been approved for the treatment of medically-refractory epilepsy.

Nonetheless, questions remain about exactly how DBS works, and new directions are likely to emerge through research on the mechanisms that underlie its benefits.

The DBS System

The DBS system consists of three components: the lead, the extension, and the implantable pulse generator (IPG). The "lead" (also called an electrode)—a thin, insulated wire—is inserted through a small opening in the skull and implanted into the brain (Figures 1-3).

The tip of the electrode is positioned within the specific brain area depending on the disorder. The "extension" is an insulated wire that is passed under the skin of the head, neck, and shoulder, connecting the lead to the IPG.

The IPG is a surgically-implanted, battery-operated medical device (the "battery pack") that is similar to a heart pacemaker and has the approximate size of a stop-watch. It delivers electrical stimulation to specific areas in the brain that control movement, blocking the abnormal nerve signals that cause symptoms.

The IPG is usually implanted under the skin near the collarbone; in some cases, it may be implanted lower in the chest or under the skin over the abdomen.

Once the system is in place, and after a period of healing post-surgery, the device is programmed and tuned to sets of parameters that work best for each person over several visits with a neurologist.

The therapy works by delivering electrical pulses from the IPG along the extension wire and the lead, and into the brain. These pulses change the brain's electrical activity pattern at the target site to reduce motor symptoms.

Treatment rationale

Patients with severe TS, resistant to medical and behavioral therapy, may benefit from the application of DBS. An important challenge and limitation in evaluating the evidence related to this procedure in TS is that, even in expert DBS centers, few operations per year are performed.

Furthermore, there is limited information from randomized clinical trials for analysis and interpretation.

Surgery candidates and patients' selection Sydenham's chorea (SC);

Surgery candidates should have a DSM-5 diagnosis of TS with severe motor and vocal tics that, despite exhaustive medical and behavioral treatment trials, result in significant impairment.

DBS should be offered to patients only by experienced DBS centers after evaluation by a multi-disciplinary team.

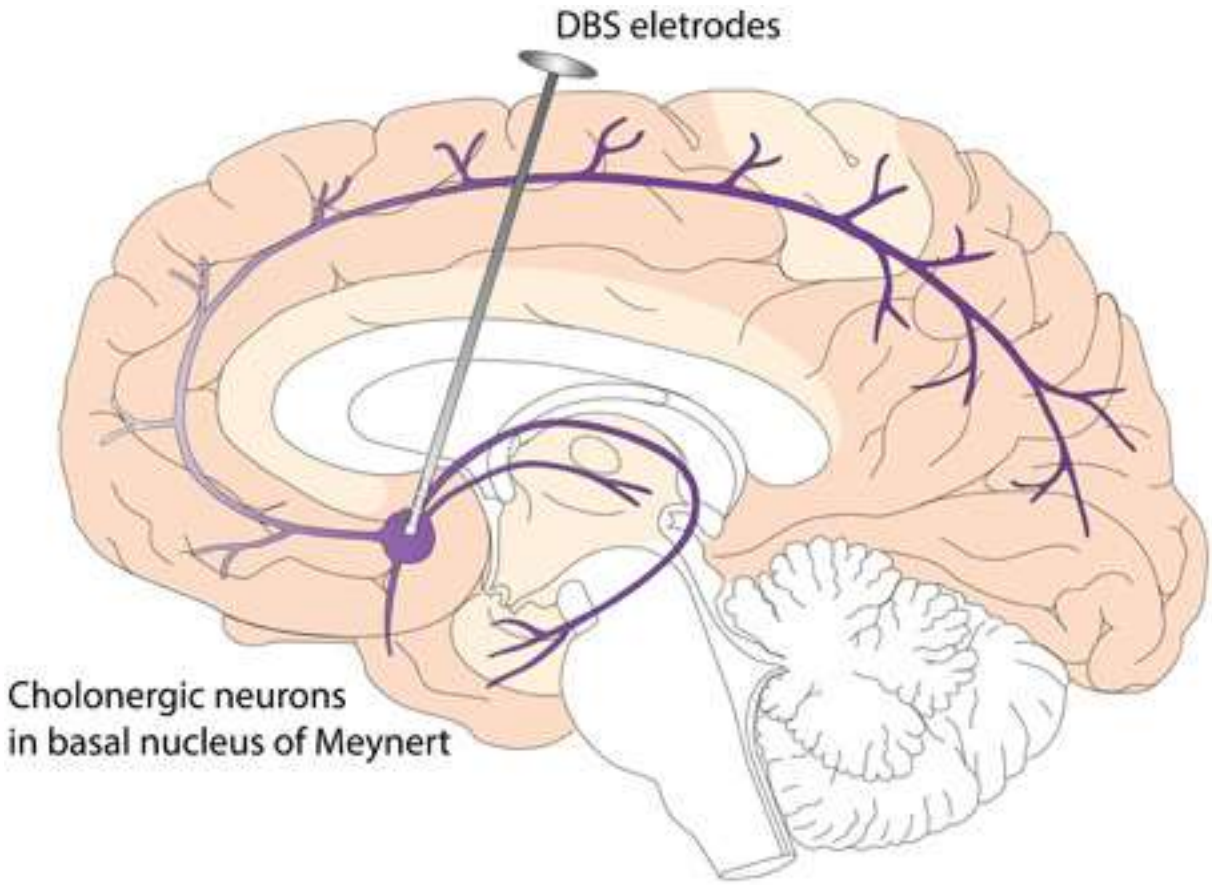
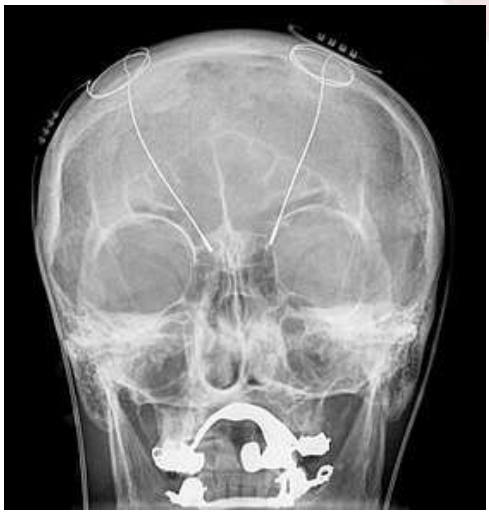


Figure 1: Pictorial showing an inserted deep brain stimulation electrode



(Bright white areas around the maxilla and the mandibles represent metal dentures that are unrelated to the DBS device)

Figure 2: DBS-probes are shown in an X-ray of the skull

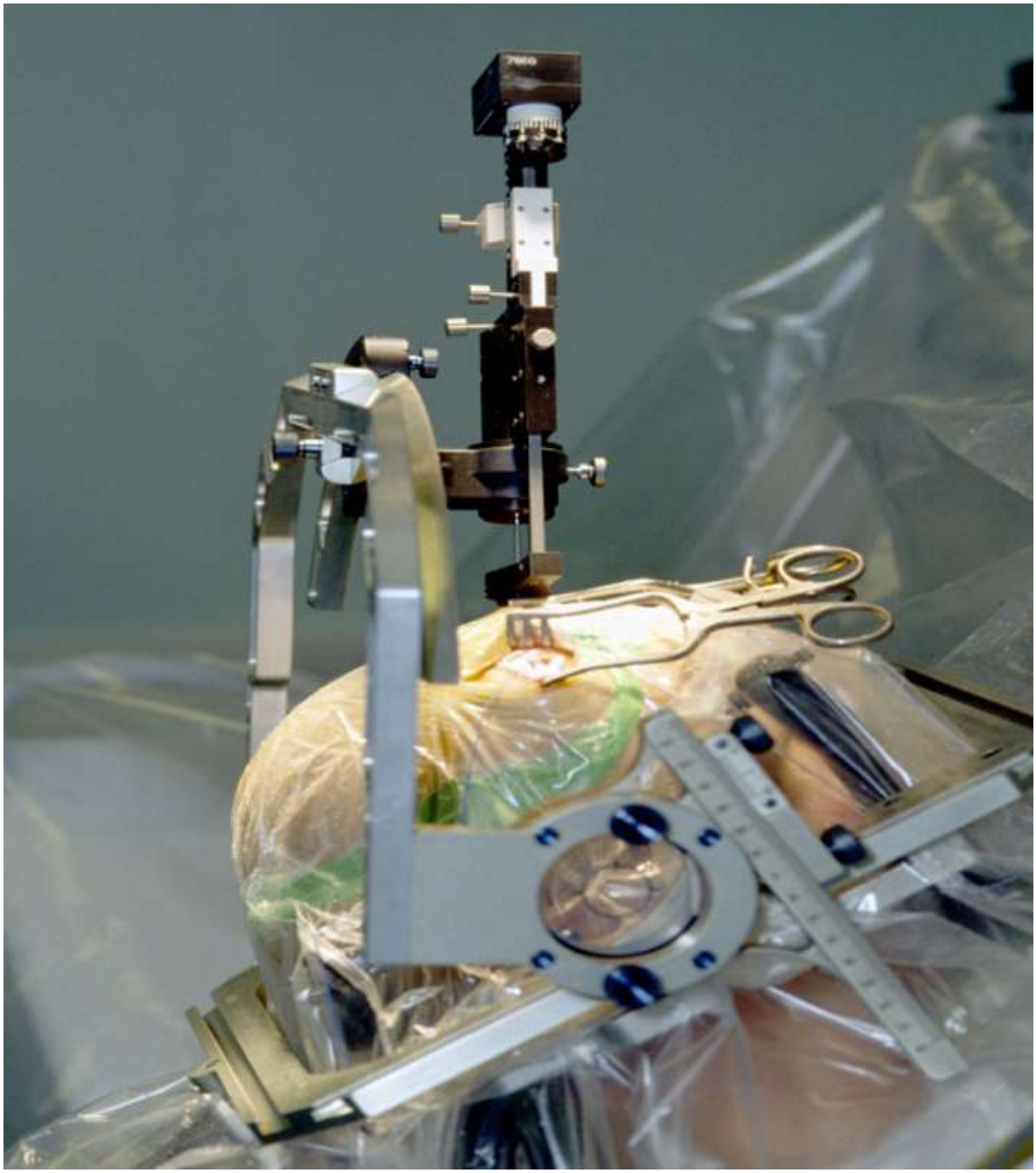


Figure 3: Placement of an electrode into the brain

(The head is stabilized in a frame for stereotactic surgery)

Rigorous pre-operative and post-operative outcome measures of tics and associated co-morbidities should be used. Tics

and co-morbid neuropsychiatric conditions should be optimally treated per current expert standards, and tics should be the major cause of disability. Psychogenic tics, embellishment, and malingering should be recognized and addressed. A multidisciplinary team approach for screening is employed. A local ethics committee (LEC) or institutional review board (IRB) should be consulted for consideration of cases involving persons younger than 18 years of age, as well as in cases with urgent indications.

TS patients represent a unique and complex population, and studies reveal a higher risk for post-DBS complications. Successes and failures have been reported for multiple brain targets; however, the optimal surgical approach remains unknown. Though still evolving, DBS is a promising approach for a subset of medication-refractory and severely-affected patients. Appropriate patient selection is one of the most important predictors of success of DBS treatment, making multi-disciplinary evaluation essential. Because of the complexity of the patient population, centers performing DBS have been encouraged to screen candidates pre-operatively and to follow them post-operatively. There has been concern about high risk of suicide and other negative psychiatric sequelae in patients with TS not screened and monitored for depression, anxiety, and bipolar tendencies.

Treatment recommendations

When DBS is applied in TS, the American Academy of Neurology (AAN) has issued in 2019 the recommendations indicated in Table 11.

Recommendation #	Level	Physician's role
13a	A	Must use a multidisciplinary evaluation (psychiatrist or neurologist, neurosurgeon, and neuropsychologist) to establish when the benefits of treatment outweigh the risks of prescribing DBS for medication-resistant motor and phonic tics
13b	B	Should confirm the DSM-5 diagnosis of TS and exclude secondary and functional tic-like movements when considering DBS for medication-resistant tics
13c	A	Must screen patients preoperatively and follow patients post-operatively for psychiatric disorders that may impede the long-term success of the therapy
13d	A	Must confirm that multiple classes of medication (antipsychotics, dopamine depleters, α2 agonists) and behavioral therapy have been administered (or are contra-indicated) before prescribing DBS for tics
13e	C	May consider DBS for severe, self-injurious tics, such as severe cervical tics that result in spinal injury

Source: AAN Recommended TS Guidelines (2019)

Table 11: Recommendations for deep brain stimulation (DBS) for tics in the TS setting

Stimulated brain regions

There is no consensus on the optimal brain target for the treatment of tics. Different key structures and different brain targets have been defined for DBS as the thalamus (centromedian-parafascicular complex region and subthalamic nucleus), globus pallidus (ventral and dorsal internus, externus, and anteromedial), nucleus accumbens (ventral capsular), basal ganglia, and vagus nerve. There is insufficient evidence to determine the efficacy of DBS of the thalamus in reducing tic severity.

Figure 4 shows the active DBS contact lesions in the bilateral atlas space. The circles represent an active DBS contact colored by its intended structural DBS target region. The active contacts are usually all found to be located relatively near the intended target nuclei.

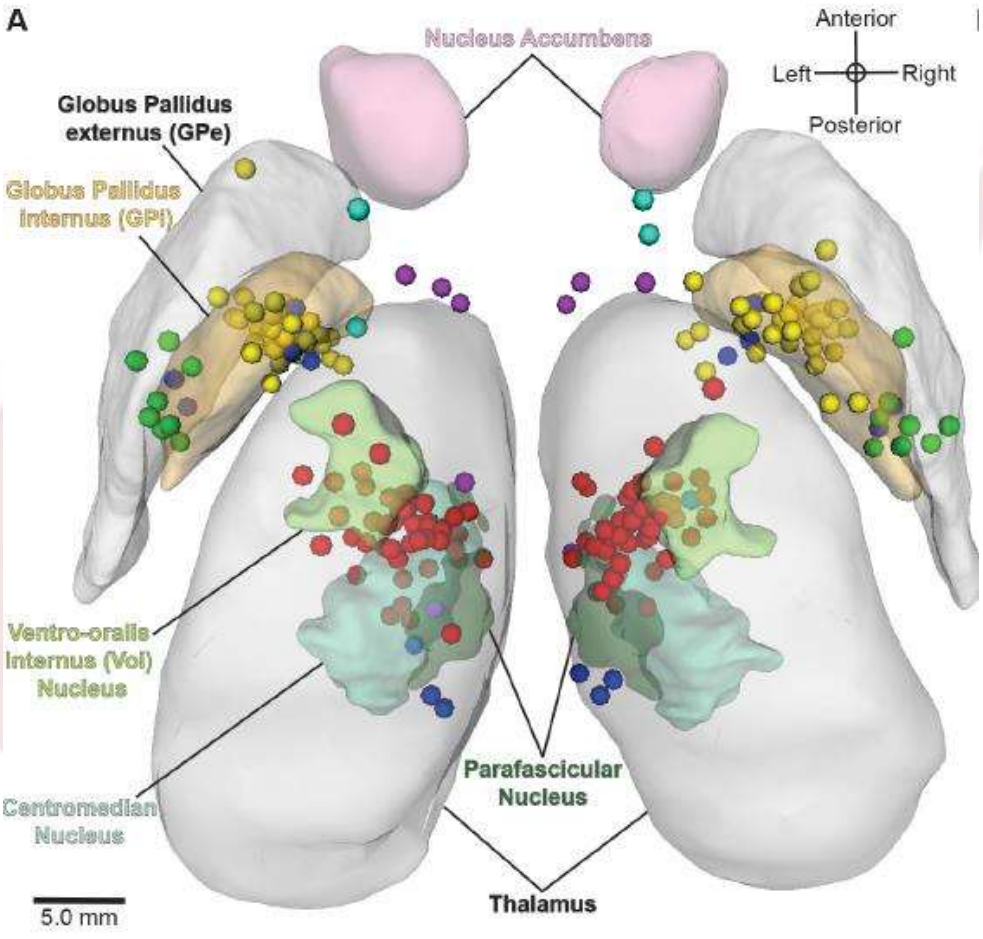


Figure 4: Active DBS contact lesions in the bilateral atlas space (3D superior view)

Treatment benefits, risks and complications

DBS is a surgical procedure that involves minimal permanent surgical changes to the brain and is minimally invasive. There is a low chance the placement of the stimulator may cause bleeding or infection in the brain. Nonetheless, it carries some associated risk. Complications may include bleeding and swelling of brain tissue, headaches, seizures, and temporary pain following the surgery. Complications resulting from infection and removal of hardware may be due to mechanical stress from the device, but are generally reversible. Also, the hardware may erode or break down with use, requiring surgery to replace parts of the device. If the DBS causes unwanted side effects or newer, more promising treatments develop in the future, the IPG can be removed and the DBS procedure halted. Also, if the person's condition changes, stimulation from the IPG is easily adjustable without further surgery. Data on harms related to the use of DBS

can be found in the complete and unabridged practice guideline.

The largest available randomized clinical trials (RCT) of DBS have revealed benefits on motor and phonic tics for the ventral globus pallidus internus and the centromedian thalamic region target; however, these studies have raised methodological concerns that need to be addressed in future trials. There is little information on the effects of DBS on psychiatric co-morbidities and on the efficacy of DBS in children with TS.

Prognosis following the procedure

DBS may reduce the number of tics over time. However, it changes the brain firing pattern but does not slow the progression of the neurodegeneration. Despite small patient numbers, the procedure remains a valid option for medically intractable patients. Different brain targets result in comparable improvement rates, indicating a modulation of a common network. Future studies might focus on a better characterization of the clinical effects of distinct regions, rather than searching for a unique target.

International DBS Registry

An international DBS Registry has been developed to collect data on DBS outcomes in patients with TS implanted in various centers. It exists under the name International Tourette syndrome DBS Public Database and Registry (ITS-DBS-PDR). The Registry also collects information about response to non-standardized selection criteria, various brain targets, differences in hardware, and variability in the programming parameters used.

Repetitive transcranial magnetic stimulation (rTMS)

rTMS is an emerging therapeutic modality for seizure suppression. Despite being considered a safe technique, it carries the risk of inducing seizures among other milder adverse events, and thus, its safety in the population should be continuously assessed. Several research groups conducted such studies of the safety and tolerability of rTMS in patients. They estimated the risk of seizures and other adverse events during or shortly after rTMS application. They concluded that the atypical seizure happened during high-frequency rTMS with maximum stimulator output for speech arrest, clinically arising from the region of stimulation. Further, the risk of seizure induction in patients undergoing rTMS is small and the risk of other adverse events is similar to that of rTMS applied to other conditions and to healthy subjects. Nonetheless, these results should be interpreted with caution. The similarity between the safety profiles of rTMS applied to the population with TS and to individuals without TS supports further investigation of rTMS as a therapy.

Transcranial electrotherapy (TCE)

Recent imaging data suggest that the pattern of functional connectivity in cortico-basal ganglia networks is disrupted in TS patients and could reflect a defect in brain maturation. However, regions involved in the immediate genesis of tics remain unknown since it is difficult to capture on line the cortical changes associated with tic generation using imaging techniques due to moving artifacts. Moreover, tics are much more frequent in everyday life conditions than in the artificial conditions of a laboratory. The aims of the various trans-cranial direct current stimulation (TDCS) studies are briefly summarized below.

Cortical activity changes

Cortical activity changes occurring before tic occurrence are analyzed by using long duration recording of encephalographic activity (EEG) in ecological conditions through Holter EEG techniques (24-hour recordings). Recordings are performed on patients with a severe form of TS. EEG changes are correlated to event markers, voluntarily monitored by

patients or automatically recorded (accelerometers for motor tics). EEG epoch centered on tics are subsequently compared to similar epochs without tics. The occurrence of tics is also correlated with neurovegetative markers of emotions such as RR interval ECG variability and skin resistivity changes. The ultimate goal is to define a potential therapeutic target of tics for chronic cortical stimulation.

Effects of rhythmic pulses

The effects of rhythmic pulses of electrical stimulation delivered to the wrist are examined when treating tics in people with TS and CTD. This type of electrical stimulation, known as median nerve stimulation (MNS), can substantially reduce tics and related urges during stimulation. The primary hypothesis is that active rhythmic MNS will lead to a reduction in tic severity compared to a placebo condition. The secondary hypothesis is that MNS will also have a positive beneficial effect on urges, impairment, well-being and co-occurring OCD symptoms compared to both sham stimulation and no stimulation.

Sensory over-responsive manifestation (SORM)

SORM, the most pervasive sensory manifestation of TS, is defined as excessive behavioral response to commonplace environmental stimuli. It is associated with avoidant behavior and functional impairment. More than 50% of children and 80% of adults with TS report SORM. Across age groups, SORM is positively correlated with severity of tics, psychiatric symptoms, and negatively correlated with quality of life (QOL). Thus, SORM is an integral facet of the TS phenotype, one intertwined with core elements of the disorder and worse QOL. Enhanced understanding of SORM's neurobiological basis is crucial to a more complete knowledge of TS pathophysiology.

Two neurophysiological mechanisms are implicated in SORM: sensory-gating impairment and autonomic hyper-arousal. Sensory-gating is the physiologic process whereby redundant environmental stimuli are filtered out in the early stages of perception. Impairment of sensory gating gives rise to altered sensory perception.

Autonomic hyper-arousal is a state of excessive sympathetic tone and/or reduced parasympathetic tone, which hampers behavioral adaptation to sensory input. In TS, multiple lines of evidence suggest both sensory gating and autonomic function are impaired.

Median nerve stimulation (MNS)

Rhythmic 12-Hz peripheral stimulation of the median nerve reduces tic frequency and severity. It evokes synchronous contralateral EEG activity over primary sensorimotor cortex, whereas arrhythmic stimulation at the same mean rate does not. MNS at 12-Hz created small but statistically significant effects on initiation of voluntary movements. Importantly, this stimulation does not meaningfully impair concentration, suggesting that the effect does not operate through simple distraction. At 10 Hz, in some patients, MNS may significantly reduce the number of tics and their severity.

Applications in psychiatric diseases

Tic disorders is recognized as a neuropsychiatric disease. As a non-invasive therapy, cranial electrotherapy stimulation (CETS) may be applied in various areas with few side effects.

Continuous theta-burst stimulation (cTBS)

cTBS is relatively safe and effective, and its efficacy in psychiatric diseases has been gradually recognized. However, the results of current researches of tic disorder treatment are varied and the evaluation method is relatively simple. cTBS under functional

MRI-guided stimulation is employed in patients with tics to explore individualized treatment parameters, including stimulation frequency, intensity, type, time, and stimulation target. Based on DBS studies that reported that the medial globus pallidus (MGP) showed an obvious curative effect, a deep brain area can be modulated indirectly by a superficial target via functional connectivity. Therefore, cTBS stimulates the superficial target in the supplementary motor area (SMA) and the lateral motor area (LMA). Combined with clinical symptoms and neuroimaging, the therapeutic effect of cTBS in children with tic disorder may provide a new therapeutic method and a better therapeutic effect for the disease.

Vagus nerve stimulation (VNS) to improve behavioral control

Non-invasive electrical stimulation of the vagus nerve via transcutaneous vagus nerve stimulation (tVNS) has been studied for its effects on cognitive functions, and inhibitory and tic control in patients with tic disorders. Taking into account the role that GABA plays in inhibitory control, the alteration of GABA neurotransmission and the possibility to increase its release with tVNS may improve behavioral control in tic disorders.

Summary and Conclusions

Each person with TS requires an individualized treatment plan. Not everyone with TS will need medical treatment and medical treatment needs can vary over time. While there is no cure for TS, there are a number of medical treatments that can be effective at reducing tics or helping to manage co-occurring conditions such a ADHD and OCD. The goal is not to eliminate but alleviate symptoms to a point that they are no longer causing distress to the patient or interfere with function. There is no one medication that is helpful to all people with TS, nor does any medication completely eliminate symptoms. If tic symptoms are mild and do not cause impairment, there may be no need for treatment. If, however, they interfere with daily functioning, there are effective medications and other treatments. Some medications may have or cause side effects and should be carefully managed. The side effects need to be considered carefully when deciding whether or not to use any medication as adverse effects may be more disturbing than the symptoms being treated with medication. Medication types include: Anti-hypertensives, antipsychotics, antidepressants/ anti-anxiety medicines, anti-seizure medicines, neuroleptics, stimulants, and others. All the known medications have been described and abundantly discussed with Facts Sheets provided for those FDA-approved ones. Nonetheless, while there is evidence to support the efficacy of several treatments, knowledge gaps remain including the necessity of randomized controlled trials. of interventions for tics to further evaluate both long-term efficacy and safety.

Complementary medicine approaches (acupuncture, allergy testing and control, cannabis-based medications, dietary modification, neurofeedback, intravenous immunoglobulin, plasma exchange) have popular appeal but no proven benefit in the management of TS. Orphan, repurposed, off-label, and compassionate medicines have also been presented. Health technology assessments are needed to ascertain whether any given medicine is effective/ cost effective in comparison to existing medicines available. The ultimate goal is to have authorized medicines available, affordable, and accessible for rare disease patients.

Surgery can be an optional treatment in those rare cases of patients severely disabled by TS who do not improve using standard approaches. It includes deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), or transcranial direct current stimulation (TDCS). Surgical procedures are administered more frequently in adults and remain investigational in children. They need to be further investigated and used only at expert centers. The

rigorous selection of candidate patients is one of the most important predictors of success of DBS treatment, making multi-disciplinary evaluation essential. However, there is no consensus on the optimal brain target for the treatment of tics. Three different key structures are defined for DBS, the medial portion of the thalamus, the globus pallidus internus and the anterior limb of the internal capsule/nucleus accumbens. DBS changes the brain firing pattern but does not slow the progression of the neurodegeneration. Future studies might focus on a better characterization of the clinical effects of distinct regions, rather than searching for a unique target. While considered a safe technique, the emerging therapeutic modality for seizure suppression represented by 'repetitive transcranial magnetic stimulation' (rTMS) carries nonetheless the risk of inducing seizures, among other milder adverse events, and thus, its safety should be continuously assessed.

Recent transcranial electrotherapy (TCE) imaging data suggest that the pattern of functional connectivity in cortico-basal ganglia networks is disrupted in TS patients and could reflect a defect in brain maturation. The effects of median nerve stimulation (MNS) can substantially reduce tics and related urges during stimulation. The most pervasive sensory manifestation of TS is sensory over-responsivity, which is associated with avoidant behavior and functional impairment. It is an integral facet of the TS phenotype, one intertwined with core elements of the disorder and worse quality-of-life. Enhanced understanding of its neurobiological basis is crucial to a more complete knowledge of TS pathophysiology.

Continuous theta burst stimulation (cTBS) is relatively safe and effective, and its efficacy in psychiatric diseases has been gradually recognized. However, the results of current researches of tic disorder treatment are varied. It may provide a new therapeutic method for children and a better therapeutic effect for the disease.

Appendix - Facts Sheets for FDA-approved TS drugs

I have identified the following 42 drugs (and counting) developed (some in development) for TS:

1. Acetylcysteine (N-)
2. *Aripiprazole (Abilify) (in additional clinical trials)
3. Atomoxetine (in additional clinical trials)
4. Baclofen
5. Benzodiazépine (an anxiolytic)
6. Botulinum
7. Clonidine (antihypertensive; in additional clinical trials)
8. Deprenyl
9. Desipramine
10. Dronabinol + PEA (in additional clinical trials)
11. Ecopipam (in additional clinical trials)
12. Guanfacine (antihypertensive)
13. *Haloperidol (Haldol) (an anti-psychotic)
14. KAPPRA
15. Levitiracetam
16. Mecamylamine
17. Methylphenidate
18. Metoclopramide
19. Nicotine
20. Omega -3 fatty acids (in additional clinical trials)
21. Ondansetran
22. *Pimozide (Orap)
23. Pramipexole (in additional clinical trials)
24. Quantacine (in additional clinical trials)
25. Riluzole
26. Risperidone (a neuroleptic)
27. Selective serotonin re-uptake inhibitors (an anti-dpressant)
28. Serine (D-)
29. Tetrabenazine (in additional clinical trials)
30. (Delta-9) Tetrahydrocannabinol
31. Topiramate
32. Yi-GAN SAN

33. Ziprasidone, and others in additional clinical trials:
34. ABX-1431
35. CPP-109
36. EPI-743
37. (mini-)FMT-Dt-N-27/1350
38. NBI-98854
39. PF-03654746
40. PF-04457845
41. SCI-110
42. TEV-50717

and others.

(*) sole (U.S.) FDA-approved medicines for use in the U.S.A.

It will not be practical to provide here the Facts Sheets for all of them. I will limit myself solely to those FDA-approved drugs.

Aripiprazole (Abilify)

Uses

Aripiprazole is used to treat a mental/mood disorder called schizophrenia. This medication can decrease hallucinations (hearing/seeing things that are not there) and improve concentration. It also helps to think more clearly, feel less nervous, and take a more active part in everyday life. Some brands of this medication are also used to treat bipolar disorder. It can help to decrease extreme changes in mood and help feel less agitated. The extended-release form is a long-acting psychiatric medication known as an atypical antipsychotic by helping to restore the balance of certain natural substances in the brain.

Side Effects

Rare: Rise in blood sugar level can cause or worsen diabetes. In some cases, tardive dyskinesia may be permanent and unusual uncontrolled movements (especially of the face, mouth, tongue, arms, or legs). It may also cause a very serious condition called 'neuroleptic malignant syndrome' (NMS) with such symptoms: Fever, muscle stiffness/ pain/ tenderness/ weakness, severe tiredness, severe confusion, sweating, fast/irregular heartbeat, dark urine, signs of kidney problems (such as change in the amount of urine). Allergic reaction to this drug is rare.

Not serious: Dizziness, lightheadedness, drowsiness, nausea, vomiting, tiredness, excess saliva/ drooling, blurred vision, weight gain, constipation, headache, and trouble sleeping may occur. Dizziness and lightheadedness can increase the risk of falling.

Other products that cause drowsiness are opioid pain or cough relievers (*Codeine, Hydrocodone), alcohol, Marijuana (Cannabis), drugs for sleep or anxiety (Alprazolam, Lorazepam, Zolpidem), muscle relaxants (Carisoprodol, Cyclobenzaprine), or antihistamines (Cetirizine, Diphenhydramine).*

Serious: Fainting, mental/mood changes (such as increased anxiety, depression, suicidal thoughts), trouble swallowing, restlessness (especially in the legs), shaking (tremor), muscle spasm, mask-like expression of the face, seizures, trouble controlling certain urges (such as gambling, sex, eating or shopping), interrupted breathing during sleep.

Very serious: Serious allergic reactions include: Fever, swollen lymph nodes, rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Precautions

This product may contain inactive ingredients, which can cause allergic reactions or other problems depending on medical history, especially of:

- Problems with blood flow in the brain (such as cerebrovascular disease, stroke).

- Diabetes (including family history).

- Heart problems (such as low blood pressure, coronary artery disease, heart failure, irregular heartbeat).

- Nervous system problems (such as dementia, NMS, seizures).
- Obesity.

- Low white blood cell count (including history of low white blood cell count caused by medications).

- Swallowing problems.

- Breathing trouble during sleep (sleep apnea).

This drug may also cause dizziness, drowsiness or vision blur. Alcohol or marijuana (cannabis) can also cause dizziness, drowsiness. It may also make one sweat less and more likely to get heat stroke. Liquid preparations of this product may contain sugar so caution is advised for diabetics.

Notes for:

• **Older adults:** More sensitive to side effects, especially seizures, drowsiness, dizziness, lightheadedness, confusion, tardive dyskinesia, swallowing problems, and other serious (rarely fatal) side effects.

• **Females:** During pregnancy, this medication should be used only when clearly needed. It passes into breast milk. Babies born to mothers who have used this drug during the last 3 months of pregnancy may rarely develop symptoms including muscle stiffness or shakiness, drowsiness, feeding/breathing difficulties, or constant crying.

Interactions with other drugs

Drug interactions may change how medications work or increase the risk for serious side effects. This drug may interact with *Metoclopramide*.

Haloperidol (Haldol)

Uses

Haloperidol is a psychiatric medication (anti-psychotic-type) that works by helping to restore the balance of certain natural substances in the brain (neurotransmitters). It has several uses:

• **Treat uncontrolled movements and outbursts of words/sounds related to TS.**

• **Treat certain mental/mood disorders:** Schizophrenia and schizoaffective disorders. It helps to think more clearly, feel less nervous, and take part in everyday life.

• **Treat severe behavior problems:** in hyperactive children when other treatments or medications have not worked.

• **Decrease negative thoughts and hallucinations.**

• **Help prevent suicide: in people who are likely to harm themselves.**

• **Reduce aggression and the desire to hurt others.**

Side effects

Rare: This medication may rarely cause a condition known as 'tardive dyskinesia' that, in some cases, may be permanent and a very serious condition called 'neuroleptic malignant syndrome' (NMS) that manifsets itself by the following symptoms: fever, muscle stiffness/pain/tenderness/weakness,severe tiredness,

severe confusion, sweating, fast/irregular heartbeat, dark urine, and signs of kidney problems (such as change in the amount of urine). It may also increase the level of prolactin (a certain chemical made by the body).

Further, *Haloperidol* may cause a condition called 'QT prolongation' that affects the heart rhythm, which can rarely entail serious (rarely fatal) fast/irregular heartbeat and other symptoms (such as severe dizziness, fainting) that need medical attention right away. The risk of QT prolongation may be increased if taking certain other drugs (such as diuretics/"water pills"), certain other medical conditions exist (heart problems such as heart failure, slow heartbeat, QT prolongation in the EKG, a family history of such problems, or sudden cardiac death), other conditions such as severe sweating, diarrhea, or vomiting. Low levels of potassium or magnesium in the blood may also increase this risk.

Not serious: Many people using this medication do not have serious side effects. Nonetheless, dizziness, lightheadedness, drowsiness, difficulty urinating, sleep disturbances, headache, or anxiety, facial/ muscle twitching (such as tongue thrusting, chewing movements, puffing or puckering of the mouth), or uncontrollable shaking may occur. Dizziness and lightheadedness can increase the risk of falling. Other possible side effects can occur: muscle spasm/stiffness, shaking (tremor), restlessness, mask-like facial expression, drooling.

Serious: Serious side effects may include: nausea/vomiting that does not stop, stomach/abdominal pain, yellowing of eyes/skin, seizures, signs of infection (such as sore throat that does not go away, fever), slow heartbeat, severe dizziness, chest pain, or fainting.

Very serious: Allergic reaction to this drug is rare, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing. Allergy or cough-and-cold products may contain ingredients that cause drowsiness.

Notes for:

• **Older adults:** May be especially more sensitive to drowsiness, dizziness, lightheadedness, difficulty urinating, and heart effects such as QT prolongation. Drowsiness, dizziness, and lightheadedness can increase the risk of falling.

• **Males:** The increase in prolactin may result in decreased sexual ability, inability to produce sperm, or enlarged breasts. Rarely, males may have a priapism (painful or prolonged erection lasting 4 or more hours).

• **Females:** The increase in prolactin may result in unwanted breast milk, missed/stopped periods, or difficulty becoming pregnant.

Precautions

This product may contain inactive ingredients, which can cause allergic reactions or other problems depending on medical history, especially of:

- Severe CNS depression (a certain severe nervous system problem).
- Parkinson's disease.
- Bipolar disorder.
- Difficulty urinating (for example, due to prostate problems).
- Glaucoma.
- Heart problems (such as angina).
- Overactive thyroid (hyperthyroidism).

- Seizures.
- Low white blood cell count.

This drug may cause dizziness or drowsiness (also caused by alcohol or marijuana/cannabis), sweat less, more likely to get heat stroke.

During pregnancy, this medication should be used only when clearly needed. It passes into breast milk and could have undesirable effects on a nursing infant. Babies born to mothers who have used this drug during the last 3 months of pregnancy may rarely develop symptoms including muscle stiffness or shakiness, drowsiness, feeding/breathing difficulties, or constant crying.

Interactions with other drugs

Drug interactions may change how medications work or increase the risk for serious side effects. Some products that may interact with *Haloperidol include: Cabergoline, Ketoconazole, Lithium, Methyldopa, drugs for Parkinson's disease (such as Levodopa and Carbidopa, Selegiline), Paroxetine, Pergolide, Quinupristin/Dalfopristin, Saquinavir.*

Many drugs besides Haloperidol may affect the heart rhythm (QT prolongation), including *Amiodarone, Dofetilide, Pimozide, Quinidine, Sotalol, Procainamide, macrolide antibiotics (such as Erythromycin), among others. Other products that cause drowsiness such as opioid pain or cough relievers (such as Codeine, Hydrocodone), alcohol, marijuana (cannabis), drugs for sleep or anxiety (such as Alprazolam, Lorazepam, Zolpidem), muscle relaxants (such as Carisoprodol, Cyclobenzaprine), or antihistamines (such as Cetirizine, Diphenhydramine).*

Pimozide

Uses

This medication is used to reduce uncontrolled movements (motor tics) or outbursts of words/sounds (vocal tics) caused by Tourette's syndrome. It works by decreasing the activity of dopamine (a natural substance in the brain). It should only be used if symptoms cause severe problems in everyday life and other medicines or treatments have not been effective.

Side Effects

Rare: This drug may cause muscle/nervous system problems (extrapyramidal symptoms-EPS). stiff muscles, severe muscle spasms/cramping (such as twisting neck, arching back, eyes rolling up), restlessness/ constant need to move, shaking (tremor), slow/shuffling walk, drooling/trouble swallowing, mask-like expression of the face. It may also cause tardive dyskinesia that, in some cases, may be permanent.

Other drugs, such as stimulant medications (Methylphenidate, Dextroamphetamine), may occasionally worsen tics.

Not serious: Drowsiness, dizziness, lightheadedness, dry mouth, blurred vision, tiredness, or weakness may occur.Dizziness and lightheadedness can increase the risk of falling. Other products that cause drowsiness include: *Alcohol, Marijuana (Cannabis), antihistamines (Cetirizine, Diphenhydramine), drugs for sleep or anxiety (Alprazolam, Diazepam, Zolpidem), muscle relaxants, and opioid pain relievers (Codeine).*

Serious: Pimozide may cause neuroleptic malignant syndrome (NMS) as manifested by the following symptoms: Fever, muscle stiffness/ pain/ tenderness/ weakness, severe tiredness, severe confusion, sweating, fast/irregular heartbeat, dark urine, and signs of kidney problems (such as change in the amount of urine).

Very serious: Rare as manifested by symptoms of a

serious allergic reaction, including: Rash, itching/ swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing. Allergy or cough-and-cold products may contain ingredients that cause drowsiness.

Precautions

An electrocardiogram (EKG) and laboratory tests may be ordered before starting this medication to find out any risk for heart rhythm problems from Pimozide.

In rare cases, Pimozide may increase the level of prolactin (a certain chemical made by the body).

Notes for:

• **Males:** The increase in prolactin may result in decreased sexual ability, inability to produce sperm, or enlarged breasts.

• **Females:** The increase in prolactin may result in unwanted breast milk, missed/stopped periods, or difficulty becoming pregnant.

Interactions with other drugs

Drug interactions may change how medications work or increase the risk for serious side effects. Some products that may interact with this drug include: Anticholinergic/antispasmodic drugs (examples: Atropine, Dicyclomine, Scopolamine) and drugs that increase the amount of dopamine in the body (examples: *Bromocriptine, Cabergoline, Levodopa, Pergolide, Ropinirole*).

Other medications can affect the removal of Pimozide from the body, which may affect how it works (examples: *Aprepitant; Azole antifungals such as Ketoconazole, Itraconazole; HIV protease inhibitors such as Nelfinavir; Nefazodone; SSRI antidepressants such as Fluvoxamine, Paroxetine, Sertraline; Ritonavir; Zileuton*, among others).

Many drugs besides Pimozide may affect the heart rhythm (QT prolongation). Examples include *Amiodarone, Citalopra / Escitalopram, Chlorpromazine, Dofetilide, Procainamide, Quinidine, Ranolazine, Sotalol, macrolide antibiotics (such as Clarithromycin, Erythromycin)*, among others.

References

1. Fymat AL (2023). “Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome”, Tellwell Talent Publishers.
2. Fymat AL (2023). “Tourette's syndrome: I. Symptomatology and etiology”, Neurol. Psychol. Res. J. 5(1):1-34
3. Fymat AL (2023). “Tourette's syndrome: II. Diagnosis and symptoms management”, Neurol. Psychol. Res. J. 5(1):1-24

On treatment in general:

4. Bergin A, Waranch HR, Brown J, Carson K, and Singer HS (1998). “Relaxation therapy in Tourette syndrome: A pilot study”. Pediatr Neurol 1998(18):136–42.
5. Bloch MH (2008). “Emerging treatments for Tourette's disorder”, Curr Psychiatry Rep 10(4):323-30. doi: 10.1007/s11920-008-0052-z.
6. Bloch M, State M, and Pittenger C (2011). “Recent advances in Tourette syndrome”, Curr Opin Neurol 24(2):119-25. doi: 10.1097/WCO.0b013e328344648c.
7. Cath DC, Hedderly T, Ludolph AG, Stern JS, Murphy T, Hartmann-Czernecki AV, Robertson MM, Martino D, Munchau A, and Rizzo R (2011). “Group EG European clinical guidelines for Tourette syndrome and other tic disorders. Part I: assessment”. Eur Child Adolesc Psychiatry 20:155–71. doi: 10.1007/s00787-011-0164-6.

8. Cavanna AE, Servo S, Monaco F, and Robertson (2009). “The behavioral spectrum of Gilles de la Tourette syndrome”, J Neuropsychiatry Clin Neurosci 21(1):13-23. doi: 10.1176/jnp.2009.21.1.13.
9. (U.S.) Centers for Disease Control and Prevention (CDC) (2019). "Tourette syndrome treatments".
10. Dion Y, Annable L, Sandor P, and Chouinard G (2002). “Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial”. J Clin Psychopharmacol 2002(22):31–9.
11. Dure LS and DeWolfe J (2006). "Treatment of tics". Adv Neurol (Review) 99:191–6.
12. Fründt O, Woods D, and Ganos C (2017). "Behavioral therapy for Tourette syndrome and chronic tic disorders". Neurol Clin Pract (Review) 7(2):148–56. doi:10.1212/CPJ.0000000000000348.
13. Fymat AL (2023). “Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome”, Tellwell Talent Publishers.
14. Fymat AL (2023). “Tourette's syndrome: II. Diagnosis and symptoms management”, Neurol. Psychol. Res. J. (in press).
15. Hollis C, Pennant M, and Cuenca J, et al. (2016). "Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: A systematic review and qualitative analysis". Health Technology Assessment. Southampton (UK): NIHR Journals Library 20(4):1–450. doi:10.3310/hta20040.
16. Jimenez-Shahed J (2020). “Medical and surgical treatments of Tourette syndrome”. Neurologic Clinics 38(2):349–66. https://doi.org/10.1016/j.ncl.2020.01.006
17. Kim BN, Lee CB, and Hwang JW, et al. (2005). “Effectiveness and safety of Risperidone for children and adolescents with chronic tic or Tourette disorders in Korea”. J Child Adolesc Psychopharmacol. 15(2):318-24.
18. Leckman JF, Hardin MT, Riddle MA, Stevenson J, Ort SI, and Cohen DJ (1991). “Clonidine treatment of Gilles de la Tourette's syndrome”. Arch Gen Psychiatry 1991(48):324–8.
19. Liu ZS, Cui YH, and Sun D et al. (2020). "Current status, diagnosis, and treatment recommendation for tic disorders in China", Front Psychiatry 11:774. doi:10.3389/fpsyt.2020.00774.
20. Ludlow AK and Rogers SL (2018). "Understanding the impact of diet and nutrition on symptoms of Tourette syndrome: A scoping review". J Child Health Care (Review) 22(1):68–83. doi:10.1177/1367493517748373.
21. Marras C, Andrews D, Sime E, and Lang AE (2001). “Botulinum toxin for simple motor tics: A randomized, double-blind, controlled clinical trial”. Neurology 56:605–10.
22. Muller-Vahl KR, Cath DC, Cavanna AE, Dehning S, Porta M, Robertson MM, and Visser-Vandewalle V (2011). “Group EG European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: Deep brain stimulation”. Eur Child Adolesc Psychiatry 20:209–17. doi: 10.1007/s00787-011-0166-4.
23. Murphy TK, Fernandez TV, and Coffey BJ, et al. (2017). “Extended-release Guanfacine does not show a large effect on tic severity in children with chronic tic disorders”. J Child Adolesc Psychopharmacol 27:762–70.
24. Peterson BS and Cohen DJ (1998). "The treatment of Tourette's syndrome: Multimodal, developmental intervention". J Clin Psychiatry (Review) 59(Suppl 1):62–74.
25. Pringsheim T, Holler-Managan Y, and Okun MS, et al. (2019). "Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic

disorders". Neurology (Review) 92(19):907–15. doi:10.1212/WNL.0000000000007467.

26. Pringsheim T, Okun MS, and Müller-Vahl K, et al. (2019). "Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders". Neurology (Review) 92(19):896–906. doi:10.1212/WNL.0000000000007466.
27. Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, Woods DW, Robinson M, Jarvie E, Roessner V, Oskoui M, Holler-Managan Y, and Piacentini J (2019). "Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders". Neurology 92:896–906. doi: 10.1212/WNL.0000000000007466.
28. Pringsheim T, Holler-Managan Y, Okun MS, Jankovic J, Piacentini J, Cavanna AE, Martino D, Muller-Vahl K, Woods DW, Robinson M, Jarvie E, Roessner V, and Oskoui M (2019). "Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders". Neurology 92:907–15. doi: 10.1212/WNL.0000000000007467.
29. Rickards H, Hartley N, and Robertson MM (1997). "Seignot's paper on the treatment of Tourette's syndrome with Haloperidol. Classic Text No. 31". Hist Psychiatry (Historical biography). 8(31 Pt 3): 433–36. doi:10.1177/0957154X9700803109.
30. Riddle MA, Geller B, and Ryan N (1993). "Another sudden death in a child treated with Desipramine" J Am Acad Child Adolesc Psychiatry 32:792–7.
31. Robertson MM (2000). "Tourette syndrome, associated conditions and the complexities of treatment". Brain (Review) 123(Pt 3):425–62. doi:10.1093/brain/123.3.425.
32. Robertson MM (2011). "Gilles de la Tourette syndrome: The complexities of phenotype and treatment". Br J Hosp Med (Lond) 72(2):100–7. doi:10.12968/hmed.2011.72.2.100.
33. Sallee FR, Kurlan R, Goetz CG, et al. (2000). "Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study". J Am Acad Child Adolesc Psychiatry 39:292–9.
34. Scahill L, Erenberg G, and Berlin CM, et al. (2006). "Contemporary assessment and pharmacotherapy of Tourette syndrome". NeuroRx (Review) 3(2):192–206. doi:10.1016/j.nurx.2006.01.009.
35. Shapiro E, Shapiro AK, and Fulop G, et al. (1989). "Controlled study of Haloperidol, Pimozide and placebo for the treatment of Gilles de la Tourette's syndrome". Arch Gen Psychiatry 46:722–30.
36. Tourette's Syndrome Study Group (2002). "Treatment of ADHD in children with tics: A randomized controlled trial". Neurology 58:527–36.
37. Verdellen C, van de Griendt J, Hartmann A, and Murphy T (2011). "Group EG European clinical guidelines for Tourette syndrome and other tic disorders. Part III: Behavioural and psychosocial interventions". Eur Child Adolesc Psych 20:197–207. doi: 10.1007/s00787-011-0167-3.
38. Woods DW, Himle MB, and Conelea CA (2006). "Behavior therapy: Other interventions for tic disorders". Adv Neurol (Review) 99:234–40.

On pharmacological treatment:

39. Fymat AL (2023). "Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome", Tellwell Talent Publishers.
40. Jankovic J, Jimenez-Shahed J, and Brown LW (2010). "A randomized, double-blind, placebo-controlled study of Topiramate in the treatment

of Tourette syndrome" J Neurol Neurosurg Psychiatry 81(1);70–3 doi:10.1136/jnnp.2009.185348.

41. Koppel BS (2017). "Cannabis in the treatment of dystonia, dyskinesias, and tics", Neurotherapeutics 12(4):788–92. doi: 10.1007/s13311-015-0376-4,
42. Maciunas RJ, Maddux BN, and Riley DE et al. (2007). "Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome", J Neurosurg. 107:1004-14.
43. Müller-Vahl KR, Schneider U, Koblenz A, and Jöbges M (2002); "Treatment of Tourette's syndrome with Delta 9-Tetrahydrocannabinol (THC): A randomized crossover trial", Pharmacopsychiatry 35(2):57–61. doi: 10.1055/s-2002-25028.
44. Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U (2003). "Treatment of Tourette syndrome with Delta-9-Tetrahydrocannabinol (Δ9-THC): No influence on neuropsychological performance", Neuropsychopharmacology 28(2). doi:10.1038/sj.npp.1300047.
45. Müller-Vahl KR, Schneider U, Prevedel H, and Theloe K (2003). "Delta 9-Tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial' The Journal of Clinical Psychiatry 64(4):459–65.
46. Müller-Vahl KR, Veit, and Münchau A (2020). "Tourette-Syndrom: Häufig eine Fehldiagnose. Deutsche Aerzteblatt 117.
47. Müller-Vahl KR, Fremer C, Beals C, Ivkovic J, Loft H, and Schindler C (2021). "Monoacylglycerol lipase Inhibition in Tourette Syndrome: A 12-week, randomized, controlled Study". Mov Disord 10.1002/mds.28681
48. Peterson BS and Cohen DJ (1998). "The treatment of Tourette's syndrome: Multimodal, developmental intervention", J Clin Psychiatry 59(Suppl 1):62–72.
49. Porta M, Sassi M, and Cavallazzi M et al. (2008). "Tourette's syndrome and role of tetrabenazine : Review and personal experience", Cl (Abstract).
50. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, Strand G, Stern JS, Termine C, and Hoekstra PJ (2011). "Group EG European clinical guidelines for Tourette syndrome and other tic disorders. Part II: Pharmacological treatment". Eur Child Adolesc Psychiatry 20:173– 96. doi: 10.1007/s00787-011-0163-7.
51. Sallee F, Kohegyi E, Zhao J, McQuade R, Cox K, Sanchez R, van Beek A, Nyilas M, Carson W, and Kurlan R (2017). "Randomized, double-blind, placebo-controlled trial demonstrates the efficacy and safety of oral Aripiprazole for the treatment of Tourette's disorder in children and adolescents." J Child Adolesc Psychopharmacol 27:771–81. doi: 10.1089/cap.2016.0026.
52. Scahill L, Leckman JF, Schultz RT, Katsovich L, and Peterson BS (2003). "A placebo-controlled trial of Risperidone in Tourette syndrome", Neurology 60:1130-5.
53. Simpson DM, Blitzer A, and Brashear A et al. (2008). "Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology", Neurology 70:1699-1706.
54. Tourette's Syndrome Study Group (2002). "Treatment of ADHD in children with tics: A randomized controlled trial" Neurology 58:527–36.
55. Verdellen C, van de Griendt J, and Hartmann A (2011). "ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other tic disorders. Part III: behavioral and

psychosocial interventions", Eur Child Adolesc Psychiatry 20:197-207.

56. Waldon K, Hill S, Termine C, Balottin U, and Cavanna AE (2013). "Trials of pharmacological interventions for Tourette syndrome: A systematic review", Behav Neurol 26:265-73.
57. Yang C, Hao Z, Zhang LL, Zhu CR, Zhu P, and Guo Q (2019). "Comparative efficacy and safety of antipsychotic drugs for tic disorders: A systematic review and Bayesian network meta- analysis". Pharmacopsychiatry 52:7–15. doi: 10.1055/s-0043-124872.
58. Yoo HK, Joung YS, Lee JS, Song DH, Lee YS, Kim JW, Kim BN, and ho SC (2013). "A multicenter, randomized, double-blind, placebo-controlled study of Aripiprazole in children and adolescents with Tourette's disorder". J Clin Psych 74:e772–80. doi: 10.4088/JCP.12m08189.

On non-pharmacological treatment:

59. Cavanna AE, Servo S, Monaco F, and Robertson MM (2009). "The behavioral spectrum of Gilles de la Tourette syndrome". J Neuropsychiatry Clin Neurosci. 21:13–23.
60. Coffey BJ and Shechter RL (2006). "Treatment of co-morbid obsessive compulsive disorder, mood, and anxiety disorders" Adv Neurol 99:208–21.
61. Fymat AL (2023). "Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome", Tellwell Talent Publishers.
62. Houeto J and Giré P (2008). "Tics and Tourette syndrome: Diagnosis, course, and treatment principles". Presse Med 37(2 Pt 2):263–0.
63. Piacentini J, Woods DW, and Scahill L et al.,(2018). "Behavior therapy for children with Tourette disorder: A randomized controlled trial" JAMA 303:1929–37. doi:10.1001/jama.2010.607.
64. Woods DW, Himle MB, and Conelea CA (2006). "Behavior therapy: Other interventions for tic disorders", Adv Neurol 99:234–40.

On complementary and alternative treatment:

65. Black N, Stockings E, and Campbell G, et al. (2019). "Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis". Lancet Psychiatry 6(12):995–1010. doi:10.1016/S2215-0366(19)30401-8.
66. Curtis A, Clarke CE, and Rickards HE (209). "Cannabinoids for Tourette's syndrome", Cochrane Database of Systematic Reviews, 7 October 2009.
67. Fymat AL (2023). "Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome", Tellwell Talent Publishers.
68. Koppel BS (2017). "Cannabis in the treatment of dystonia, dyskinesias, and tics", Neurotherapeutics 12(4):788–92. doi: 10.1007/s13311-015-0376-4,
69. Kumar A, Duda L, Mainali G, Asghar S, and Byler D (2018). "A comprehensive review of Tourette syndrome and complementary alternative medicine". Curr Dev Disord Rep (Review) 5(2):95–100. doi:10.1007/s40474-018-0137-2.

On deep brain stimulation:

70. Ackermans L, Temel Y, Cath D, van der Linden C, Bruggeman R, Kleijer M, Nederveen P, Schruers K, Colle H, Tijssen MA, and Visser-Vandewalle V (2006). "Dutch Flemish Tourette Surgery Study Group: Deep brain stimulation in Tourette's syndrome: Two targets?" Mov Disord 21: 709–13.
71. Ackermans L, Temel Y, Bauer NJC, and Visser-Vandewalle V (2007). "Vertical gaze

palsy after thalamic stimulation for Tourette syndrome: Case report". Neurosurgery 61:E1100.

72. Ackermans L, Temel Y, and Visser-Vandewalle V (2008). "Deep brain stimulation in Tourette's syndrome". Neurotherapeutics 5:339–44.
73. Babel TB, Warnke PC, and Ostertag CB (2001). "Immediate and long term outcome after infrathalamic and thalamic lesioning for intractable Tourette's syndrome". J Neurol Neurosurg Psychiatr 70:666–71.
74. Bajwa RJ, de Lotbinière AJ, King RA, Jabbari B, Quatrano S, Kunze K, Scahill L, and Leckman JF (2007). "Deep brain stimulation in Tourette's syndrome". Mov Disord 22:1346–50.
75. Bajwa RJ, de Lotbinière AJ, King RA, Jabbari B, Quatrano S, Kunze K, Scahill L, and Leckman JF (2007)."Deep brain stimulation in Tourette's syndrome". Mov Disord. 22(9):1346-50. doi: 10.1002/mds.21398.
76. Baldermann JC, Schüller T, Huys H, Becker I, Timmermann L, Jessen F, Visser-Vandewalle V, and Kuhn J (2016). "Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis" Brain Stimul (Review) 9(2):296-304. doi: 10.1016/j.brs.2015.11.005.
77. Black KJ (2009). "Patient page: Deep brain stimulation for Tourette syndrome". Neurology 73:e87– e90.
78. Burd L, Kerbeshian PJ, Barth A, Klug MG, Avery PK, and Benz B (2001). "Long-term follow-up of an epidemiologically defined cohort of patients with Tourette syndrome". J Child Neurol 16:431-7.
79. Burdick A, Foote KD, Goodman W, Ward HE, Ricciuti N, Murphy T, Haq I, and Okun MS (2010). "Lack of benefit of accumbens/capsular deep brain stimulation in a patient with both tics and obsessive–compulsive disorder". Neurocase 16:321–30.
80. Dehning S, Mehrkens J, Müller N, and Bötzel K (2008). "Therapy-refractory Tourette syndrome: Beneficial outcome with globus pallidus internus deep brain stimulation". Mov Disord 23:1300–02.
81. Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, and Alesch F (2005). "Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: A case report". Mov Disord 20:1496–9.
82. Dueck A, Wolters A, Wunsch K, Bohne-Suraj S, Mueller J, Haessler F, Benecke R, and Buchmann J (2009). "Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe Tourette syndrome and mental retardation". Neuropediatrics 40:239–42.
83. Flaherty AW, Williams ZM, Amirnovin R, Kasper E, Rauch SL, Cosgrove GR, and Eskandar EN (2005). "Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: Technical case report". Neurosurgery 57(Suppl 4):E403.
84. Foltynie T, Martinez-Torres I, Zrinzo L, Joyce E, Cavanna A, Jahanshahi M, Limousin P, and Hariz M (2009). "Improvement in vocal and motor tics following DBS of motor GPi for Tourette syndrome, not accompanied by subjective improvement in quality of life—a case report". Mov Disord 24(Suppl 1):S497–8.
85. Fymat AL (2023). "Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome", Tellwell Talent Publishers.
86. Gallagher CL, Garell PC, and Montgomery EB (2006). "Hemi tics and deep brain stimulation". Neurology 66:E12.
87. Hariz MI and Robertson MM (2010). "Gilles de la Tourette syndrome and deep brain stimulation".
88. Eur J Neurosci. 32(7):1128-34. doi: 10.1111/j.1460-9568.2010.07415.x.

89. Hassler R and Dieckmann G (1970). "Stereotaxic treatment of tics and inarticulate cries or coprolalia considered as motor obsessional phenomena in Gilles de la Tourette's disease". Rev Neurol 123:89–100.
90. Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, Welter ML, Navarro S, Pelissolo A, Damier P, Pidoux B, Dormont D, Cornu P, and Agid Y (2005). "Tourette's syndrome and deep brain stimulation." J Neurol Neurosurg Psychiatry 76:992–5.
91. Kefalopoulou Z, Zrinzo L, and Jahanshahi M, et al. (2015). "Bilateral globus pallidus stimulation for severe Tourette's syndrome: A double-blind, randomized crossover trial". Lancet Neurol 14:595–605.
92. Kuhn J, Lenartz D, Mai JK, Huff W, Lee S, Koulousakis A, Klosterkoetter J, and Sturm V (2007). "Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome". J Neurol 254:963–5.
93. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, and Cohen DJ (1989). "The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity". J Am Acad Child Adolesc Psychiatry 28:566–73.
94. Linden van der, C, Colle H, Vandewalle V, Alessi G, Rijckaert D, and de Waele L (2002). "Successful treatment of tics with bilateral internal pallidum (GPi) stimulation in a 27-year-old male patient with Gilles de la Tourette's syndrome (GTS)". Mov Disord 17:P1130.
95. Maciunas RJ, Maddux BN, Riley DE, Whitney CM, Schoenberg MR, Ogrocki PJ, Albert JM, and Gould DJ (2007). "Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome". J Neurosurg 107:1004–14.
96. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, Porta M, Servello D, Meng FG, Kuhn J, Huys D, Baldermann JC, Foltynie T, Hariz MI, Joyce EM, Zrinzo L, Kefalopoulou Z, Silburn P, Coyne T, Mogilner AY, Pourfar MH, Khandhar SM, Auyeung M, Ostrem JL, Visser-Vandewalle V, Welter ML, Mallet L, Karachi C, Houeto JL, Klassen BT, Ackermans L, Kaido T, Temel Y, Gross RE, Walker HC, Lozano AM, Walter BL, Mari Z, Anderson WS, Changizi BK, Moro E, Zauber SE, Schrock LE, Zhang JG, Hu W, Rizer K, Monari EH, Foote KD, Malaty IA, Deeb W, Gunduz A, and Okun MS (2018). "Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep brain stimulation public database and registry." JAMA Neurol. 75:353–9. doi: 10.1001/jamaneurol.2017.4317.
97. Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, and Limousin P (2009). "Improvementof tics after subthalamic nucleus deep brain stimulation". Neurology 72:1787–9.
98. Mink JW (2009). "Clinical review of DBS for Tourette syndrome". Front Biosci 1:72-6.
99. Mink JW, Walkup J, Frey KA, Como P, Cath D, Delong, Erenberg G, Jankovic J, Juncos J, Leckman JF, Swerdlow N, Visser-Vandewalle V, and Vitek JL (2006). "Tourette Syndrome Association, Inc: Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome". Mov Disord 21:1831–8.
100. Muller-Vahl KR, Cath DC, and Cavanna AE et al. (2011). "European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: Deep brain stimulation. Eur Child Adolescents, Psychiatry 20:209-17.
101. Neimat JS, Patil PG, Lozano AM (2006). "Novel surgical therapies for Tourette syndrome." J Child Neurol 21:715–8.

102. Neuner I, Podoll K, Lenartz D, Sturm V, and Schneider F (2009). "Deep brain stimulation in the nucleus accumbens for intractable Tourette's syndrome: Follow-up report of 36 months". Biol Psychiatry 65:e5–e6.
103. Neuner I, Podoll K, Janouschek H, Michel TM, Sheldrick AJ, and Schneider F (2009). "From psychosurgery to neuromodulation: deep brain stimulation for intractable Tourette syndrome". World J Biol Psychiatry 10(4 Pt 2):366-76. doi: 10.1080/15622970802513317.
104. Okun MS, Fernandez HH, Foote KD, Murphy TK, and Goodman WK (2008), "Avoiding deep brain stimulation failures in Tourette syndrome". J Neurol Neurosurg Psychiatr 79:111–2.
105. Piedad JCP, Rickards HE, and Cavanna AE (2012). "What patients with Gilles de la Tourette syndrome should be treated with deep brain stimulation and what is the best target?", Neurosurgery 2(71):173-92.
106. Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, and Robertson MM (2009). "Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: Two-year outcome". Neurology 73:1375–80.
107. Porta M, Servello D, Sevello D, Sassi M, Brambilla A, Defendi S, Priori A, and Robertson M (2009). "Issues related to deep brain stimulation for treatment-refractory Tourette's syndrome". Eur Neurol 62:264–73.
108. Poysky J and Jimenez-Shahed J (2007). "Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome". Mov Disord 22:1366–7.
109. Rickards H, Wood C, and Cavanna AE (2008). "Hassler and Dieckmann's seminal paper on stereotactic thalamotomy for Gilles de la Tourette syndrome: Translation and critical reappraisal". Mov Disord 23:1966–72.
110. Riley DE, Whitney CM, Maddux BN, Schoenberg MS, and Maciunas RJ (2007). "Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome". Mov Disord 22:1366 author reply 1367–8.
111. Roessner V, Plessen K, Rizzo R, Skov L, Strand G, Stern J, Termine C, and Hoekstra P. "The ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other chronic tic disorders. Part II: pharmacological treatment". Eur Child Adolesc Psychiatry
112. Rotsides J and Mammis A (2013). "The use of deep brain stimulation in Tourette's syndrome". Neurosurg Focus 35(5):E4. doi: 10.3171/2013.8.FOCUS13292.
113. Schrock LE, Mink JW, Woods DW, Porta M, Servello S, Visser-Vandewalle V, Silburn PA, Foltynie T, Walker HC, Shahed-Jimenez J, Savica R, Klassen BT, Machado AG, Foote KD, Zhang J-G, Hu W, Ackermans L, Temel T, Mari Z, Changizi BK, Lozano A, Auyeung M, Kaido T, Agid Y, Welter ML, Khandhar SM, Mogilner AY, Pourfar MH, Walter BL, Juncos JL, Gross RE, Kuhn J, Leckman JF, Neimat JA, Okun MS, and the Tourette Syndrome Association (TSA) International Deep Brain Stimulation (DBS) Database and Registry Study Group (2015). "Tourette syndrome deep brain stimulation: A review and updated recommendations" Mov Disord. 30(4):448–71. https://doi: 10.1002/mds.26094.
114. Servello D, Porta M, Sassi M, Brambilla A, and Robertson MM (2008). "Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: The surgery and stimulation". J Neurol Neurosurg Psychiatry 79:136–42.
115. Servello D, Sassi M, Brambilla A, Porta M, Haq I, Foote KD, and Okun MS (2009). "De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: A multiple case report". J

Neurol 256:1533–9.

116. Shahed J, Poysky J, Kenney C, Simpson R, and Jankovic J (2007). "GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities". Neurology 68:159–60.
117. Shields DC, Cheng ML, Flaherty AW, Gale JT, and Eskandar EN (2008). "Microelectrode-guided deep brain stimulation for Tourette syndrome: within-subject comparison of different stimulation sites". Stereotact Funct Neurosurg 86:87–91.
118. Temel Y and Visser-Vandewalle V (2004). "Surgery in Tourette syndrome". Mov Disord 19:3–14.
119. Vandewalle V, van der Linden C, Groenewegen HJ, and Caemaert J (1999). "Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus". Lancet 353(9154):724.
120. Verdellen C, van de Griendt J, Hartmann A, and Murphy T. "The ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other tic disorders. Part III: Behavioural and psychosocial interventions". Eur Child Adolesc Psychiatry.
121. Vilela Filho O, Ragazzo P, Silva D, Souza J, Oliveira P, and Ribeiro T (2008). "Bilateral GPe-DBS for Tourette's syndrome" (Abstr.). Neurotarget 3:65.
122. Vilela Filho O, Ragazzo P, Souza J, Silva D, Oliveira P, Piedimonte F, and Ribeiro T (2010). "Bilateral GPe-DBS for Tourette syndrome: A double-blind prospective controlled study of seven patients" (Abstr.). In: Abstract book of the ASSFN (American Society for Stereotactic and Functional Neurosurgery), 2010 biennial meeting. Bridging the Future of Neurosurgery, New York.
123. Visser-Vandewalle V (2007). "DBS in Tourette syndrome: Rationale, current status, and future prospects". Acta Neurochir Suppl 97(Pt 2):215–22.
124. Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, Groenewegen HJ, and van der Linden C (2003). "Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome - Report of three cases". J Neurosurg 99:1094–100.
125. Visser-Vandewalle V, Ackermans L, van der Linden C, Temel Y, Tijssen MA, Schruers KR, Nederveen P, Kleijer M, Boon P, Weber W, and Cath D (2006). "Deep brain stimulation in Gilles de la Tourette's syndrome". Neurosurgery 58:E590.
126. Visser-Vandewalle V and Kuhn J (2013). "Deep brain stimulation for Tourette syndrome". Handb Clin Neurol. 116:251-8. doi: 10.1016/B978-0-444-53497-2.00020-6.
127. Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, and Jankovic J (2012). "Deep brain stimulation for Tourette syndrome: Target selection". Stereotact Funct Neurosurg (Review). 90(4): 213–24. doi:10.1159/000337776.
128. Welter M, Mallet L, Houeto J, Karachi C, Czernecki V, Cornu P, Navarro S, Pidoux B, Dormont D, Bardinet E, Yelnik J, Damier P, and Agid Y (2008). "Internal pallidal and thalamic stimulation in patients with Tourette syndrome". Arch Neurol 65:952–7.
129. Welter ML, Houeto JL, Thobois S, et al. (2017). "Anterior pallidal deep brain stimulation for Tourette's syndrome: A randomized, double-blind, controlled trial". Lancet Neurol 16:610–9.
130. Xu M, Kobets A, Du J-C, and Lennington J (2015). "Targeted ablation of cholinergic interneurons in the dorsolateral striatum produces behavioral manifestations of Tourette syndrome", Proc National Academy of Sci 112(3);893–8 (ISSN 0027-8424 et 1091-6490. doi: 10.1073/pnas. 1419533112.

131. Zabek M, Sobstyl M, Koziara H, and Dzierzecki S (2008). “Deep brain stimulation of the right nucleus accumbens in a patient with Tourette syndrome - Case report”. Neurol Neurochir Pol 42:554–5.

On transcranial magnetic stimulation:

132. Chase JH, Nahas Z, and Wassermann E et al. (2004). “A pilot safety study of repetitive transcranial magnetic stimulation (rTMS) in Tourette's syndrome.” Cogn Behav Neurol 17:109–17.
133. Fymat AL (2023). “Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome”, Tellwell Talent Publishers.

On immunology:

134. Hsu CJ, Wong LC, and Lee WT (2021). "Immunological dysfunction in Tourette syndrome and related disorders". Int J Mol Sci (Review) 22(2):853. doi:10.3390/ijms22020853.
135. Fymat AL (2023). “Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome”, Tellwell Talent Publishers.

On surgery:

136. Fymat AL (2023). “Tourette: The self-under-siege neurodevelopmental, neuropsychiatric motor syndrome”, Tellwell Talent Publishers.
137. Sassi M, Servello D, and Porta M (2009). “The impact of technological advances in neurosurgery: Historical perspectives and new developments”. Funct Neurol. 24:221–4.

On prognosis and future outlook:

138. Hassan N and Cavanna AE (2012). “The prognosis of Tourette syndrome: Implications for clinical practice”. Funct Neurol. 27(1):23-7.