

## REVIEW

### Tics and Tourette's syndrome

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#### Abstract

Tics and Tourette's syndrome are common hyperkinetic movement disorders seen mostly in the pediatric age group. Tics are defined as sudden, rapid, recurrent, nonrhythmic motor movements or vocalization, generally preceded by urge. Tourette's syndrome is defined as the presence of both motor and phonic tics for more than 1 year in patients with onset less than 18 years old. Most of these hyperkinetic movement disorders improve in adulthood. This review emphasizes the clinical pearls in the diagnosis and distinguishing it from other

movement disorders. The treatment ranges from behavioral therapies, medical management, and also surgical treatment such as deep brain stimulation that is limited to refractory patients.

**Keywords:** tics, Tourette Syndrome, hyperkinetic movement disorders, movement disorders.

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### Introduction

In 1885, the French neurologist Gilles de la Tourette, working under the mentorship of Prof. Jean Martin Charcot, coined the term '*maladie des tics*'. He observed nine patients with symptoms of childhood-onset tics, waxing, and waning severity of symptoms and premonitory urge.<sup>1</sup> Tics are defined as sudden, rapid, recurrent, nonrhythmic motor movements or vocalization, generally preceded by urge. Tics are frequently observed in the pediatric population and the frequency is higher (27%) in special education populations, compared with 19.7% in a general education sample.<sup>2</sup> In a meta-analysis of 14 studies including 420,312 subjects, Tourette's syndrome (TS) was found to have a prevalence of 1%.<sup>3</sup> The Tourette International Consortium reported the characteristics of TS patients in a large population where the age of symptom onset ranged from 2 to 21 years, with a mean of 6.4 years and male to female ratio of 4.4:1.<sup>4,5</sup> The tics are most severe at 10–12 years old and eventually improves by adolescence in about 85% of the subjects.<sup>6,7</sup> In another study, tics resolved completely in 50% of the patients while 40–45% of patients had improvement in tics by adulthood and only 5–10% of patients continued to have tics.<sup>8</sup> Chronic tics and TS are more commonly seen in males than females. The male:female prevalence ranges from 2:1 to 10:1.<sup>9</sup>

The most widely accepted criteria are those formulated for TS by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).<sup>10</sup>

1. Both multiple motors and one or more vocal tics are present at some time during the illness although not necessarily concurrently.
2. The tics may wax or wane in frequency but have persisted for more than 1 year since the first tic onset.
3. Onset is before age 18 years.
4. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or a general medical condition (e.g., Huntington's disease, postviral encephalitis).

The most common and mildest of the idiopathic tic disorders is the transient tic disorder of childhood. This can be differentiated from TS as it does not last for more than 1 year.

The goal of this review is to provide a summary of the clinical features of Tics and TS with pearls to distinguish them from other movement disorders. Also, this review summarizes the treatment modalities, including behavioral therapy, medical therapies, and deep brain stimulation, and contains 'pearls' and treatment modalities for TS. The search strategy included a PubMed search with MeSH words 'Tourette's syndrome' or 'Tics' combined with 'therapeutics' or 'treatment' or 'clinical features'. Relevant articles were selected for this review, and bibliographies of research papers were also reviewed. References were selected from the review articles too.

## Clinical Features

Proper history and phenomenology is the key for correct diagnosis as it can be challenging to differentiate between tics and other hyperkinetic disorders. Phenomenological classification of motor tics has been suggested by Jankovic and colleagues as follows: (1) clonic: tics involve only a single muscle or a group of muscles, causing a brief, jerking movement; (2) dystonic: tics are slower, causing a briefly sustained abnormal posture; and (3) tonic: tics reflect an isometric contraction, typically manifesting with a brief tension of abdominal or limb muscles.<sup>11</sup> Examples include blinking, eye rolling, head nodding, shoulder shrugging, and abdominal tightening. Dystonic tics include oculogyric movements, sustained mouth opening, blepharospasm, and torticollis. Complex motor tics represent more intricate coordinated patterns of movement involving more than one muscle group. Bending, jumping, kicking, spitting, smelling, obscene gestures (copropraxia), and elaborate repertoires of movement are examples. Phonic tics are irrelevant sounds such as sniffing, coughing, throat clearing, clicks, humming, animal sounds, or whistling. Complex phonic tics consist of more involved utterances, including words, phrases, profanity, or racial slurs (coprolalia), repetition of others' words (echolalia), or repetition of one's own words (palilalia). The differential diagnosis includes myoclonus, dystonia, athetosis, mannerisms, chorea, stereotypies, restless leg syndrome, or seizures. The sensory phenomenon of urge with improvement after the movement can also be seen in akathisia, stereotypy, and restless leg syndrome. All the hyperkinetic disorders, especially akathisia, and functional movements can be suppressed but less than tics.<sup>12</sup> If the movements are multifocal or they migrate, consider myoclonus and chorea as well. Tics may sometimes persist during sleep.<sup>13</sup> Sleep disorders are also seen in patients with TS.<sup>13</sup> There are a few cases who had severe worsening of tics after varenicline use, which is a partial  $\alpha 4\beta 2$  nicotinic acetylcholine agonist that enhances dopamine release.<sup>14</sup> Varenicline is commonly used as a smoking cessation drug and thus should also be asked about during history taking.

## Motor symptoms

The following motor symptoms may be observed:

1. Tics are sudden, repetitive, stereotyped, and nonrhythmic movements that are commonly seen in childhood.
2. Tics can be either motor or phonic depending on the symptoms. Motor tics are restricted to body movements such as head jerking, facial grimacing, or hand movements. Phonic tics are due to repetitive movements of laryngeal, pharyngeal, nasal, or respiratory muscles.
3. Tics are characterized by a premonitory urge before the motor or phonic tic with temporary relief in the urge by the tic. Patients express a premonitory urge as a sensation of the internal build-up of discomfort, tightness, or paresthesia.
4. Tics are generally suppressible, and there is a rebound phenomenon after suppression.

5. The tics tend to be exacerbated during anxiety and stress. It is possible that during stress the ability to suppress the tics is reduced.<sup>15</sup>
6. The anatomical distribution of the tics evolves with age. Also, the frequency and severity of the symptoms fluctuate in due course.

## Behavioral features

Behavioral symptoms such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are commonly seen in patients with TS and often precede motor and phonic tics as an initial manifestation of TS. OCD symptoms in children with TS became more severe at a later age and were more likely to persist than tic symptoms.<sup>7</sup> These comorbid behavioral conditions often interfere with learning and with academic and work performance. In a school-based community study in the United States of America, 21% students were found to have tics and these children had prominent behavioral symptoms such as OCD, ADHD, separation anxiety, overanxious disorder, simple phobia, social phobia, agoraphobia, mania, major depression, and oppositional defiant behavior when compared to children without tics ( $p < 0.05$ ).<sup>16</sup>

## Tourette's syndrome in adults

Jankovic and colleagues reviewed the medical records of all new TS patients who were 19 years or older on initial evaluation and compared them with 18 years or younger patients. In this study, 35 out of 43 (81.4%) had onset of tics before 18 years old (mean age at onset:  $8.5 \pm 3.4$  years), with eight (18.6%) reporting the onset after 18 years old (mean age at onset:  $37.8 \pm 13.2$  years). Only 2 out of 43 patients (4.7%) had onset of tics after 50 years of age.<sup>17</sup> These patients have different body distribution of tics, with more axial involvement of motor tics such as facial and truncal area with fewer phonic tics. There was a higher prevalence of substance abuse and mood disorders with lower rates of attention-deficit hyperactivity disorder and oppositional behavior than children with TS. Adult-onset primary dystonic tics have been described in 11 patients, where 10 patients were male and the mean age of onset was 42 years. These patients also had axial involvement, involving the cranial-cervical region and the shoulders and, less frequently, the limbs.<sup>18</sup>

## Treatment

Patient and their families should be educated regarding the natural course of TS. Most of the patients have complete or partial remission as they become older. As per the recent American Academy of Neurology (AAN) guidelines, families should be provided with all details about the natural history of this condition. This includes the information on the waxing and waning nature of the tics, the peak age of tics being 10–12 years with the majority having improvement after adolescence. Clinicians should do an assessment and evaluate for any functional impairment. If the tics are not causing any

functional impairment, then watchful waiting to start treatment is acceptable.<sup>19</sup>

Management of tics is a collaborative and individualized treatment requiring patient and family education, clinical assessment, and discussion of treatment options such as behavioral therapies, and medications' effectiveness and side effect profiles. There are three mainstay treatment options available for TS: behavioral therapy, medical therapy, and surgical treatment.

## Behavioral therapy

Comprehensive Behavioral Intervention for Tics (CBIT) is an individualized treatment program of eight or more sessions consisting of habit reversal training, relaxation training, and a functional intervention to address situations that sustain or worsen tics.<sup>20</sup> In a randomized controlled trial, 126 children with TS or chronic tic disorder were randomized to behavioral therapy (8 sessions over 10 weeks) or supportive therapy with education.<sup>21</sup> There was a significant improvement in the tics based on the YGTSS scale and also on the clinical global impression improvement scale. Treatment gains were durable, with 87% of available responders to behavior therapy exhibiting continued benefit 6 months following treatment.<sup>21</sup> A recent clinical trial explored the implications of behavioral therapy on co-occurring behavioral symptoms in TS and chronic tic disorder. In this study, behavioral therapy was compared to psychoeducation and supportive therapy in 122 patients with TS or a chronic tic disorder. There was a significant improvement of co-occurring obsessive symptoms along with tic severity.<sup>22</sup> Children (9 years old and older) and adults, maintained their treatment gains for at least 6 months.

Behavioral therapy has been proven to be beneficial in patients with adult TS as well.<sup>23</sup> In an interesting analysis of 248 patients (both children and adults) with TS or chronic tic disorder, the patients who had CBIT without tic medication showed slightly better results compared to participants who had CBIT with tic medications.<sup>24</sup> Patients in the control group had psychoeducation and support without any oral medications. These patients had the same results as the patients who received alpha2 agonist class of tic suppressing medicine. Patients who had psychoeducation and support (control group) who were already on the antipsychotic class of tic medications had poorer results than the patients who received CBIT with or without tic medicine. Unfortunately, the study does not discuss the doses of antipsychotic medication, and none of the patients were on a dopamine depletory agent such as tetrabenazine. The presence of a lifetime diagnosis of ADHD, OCD, or other anxiety disorders did not moderate treatment response to CBIT, nor did age, sex, current severity of ADHD symptoms, tic severity, or severity of premonitory urges.<sup>24</sup>

## Medical therapy

In clinical practice, CBIT remains the first-line treatment in patients who have tics and Tourette's syndrome. Medical

treatment is considered in certain situations such as unavailability of CBIT certified or trained psychologists or occupational therapists, issues with insurance coverage, noncompliance to CBIT sessions, or persistence of disabling tics with CBIT. A variety of medications are available as treatment options but the evidence for medical treatment is not robust. As per the AAN guidelines,<sup>25</sup> there was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinumtoxinA injections were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. There is high confidence that the patients need to be counseled and monitored for adverse events such as weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on the heart rate, blood pressure, and ECGs. The class of medicine is selected based on the severity of the tics and the side effect profile of the medicine based on other comorbidities such as depression, anxiety, and sleep disturbance.

### Noradrenergic agents

Noradrenergic agents are classified as either presynaptic  $\alpha_2$  adrenergic agonists (e.g., clonidine, guanfacine) or noradrenergic reuptake inhibitors (e.g., atomoxetine). Alpha-2 agonists, such as clonidine and guanfacine, are considered first-line medicine for patients with TS.<sup>26</sup> This is in spite of the fact that the level of evidence for their effectiveness is less than for antipsychotics and, also they are not FDA approved for the treatment of TS. As per the AAN guidelines, clonidine is probably more likely helpful than placebo and guanfacine is possibly more likely helpful than placebo to reduce tic severity.<sup>19</sup> The most common adverse effects of clonidine and guanfacine are sedation, bradycardia and postural hypotension, and QTc prolongation with guanfacine extended release. Abrupt withdrawal of  $\alpha_2$  adrenergic agonists may cause rebound hypertension. In a multicentric study, 'extended-release' guanfacine was not found to be beneficial when compared with the placebo.<sup>27</sup> In clinical practice, this is usually the first-line medication for the treatment of tics. Several studies have demonstrated that these drugs may be useful in the treatment of mild tics with coexisting ADHD and impulse control disorder – this is preferred as first-line medicine due to better side effect profile compared to dopamine depleters and dopamine antagonists. If there is no significant improvement in tics or the patient is experiencing adverse events, consider other classes of medications.

### Neuroleptic medications

The FDA has approved only three neuroleptic medications such as haloperidol, pimozide, and aripiprazole. Other antipsychotic agents used in the treatment of TS and chronic tic disorder are fluphenazine, risperidone, tiapride, olanzapine, sulpiride, and ziprasidone.<sup>28</sup> As per the meta-analysis on neuroleptics medications, there was no difference in the efficacy of risperidone, pimozide, haloperidol, and ziprasidone.<sup>29</sup> Typical

neuroleptics are notorious for undesirable adverse effects such as sedation, involuntary or tardive movements, weight gain, hyperprolactinemia, and parkinsonism. Atypical neuroleptics have a better side effect profile compared with typical neuroleptics. Fluphenazine has been reported to be efficacious as well. Patients had 'moderate to marked' improvement in 80.5% of patients at the initial visit and 76% at last follow-up at an optimal dose of 3.24 mg/day (range, 0.5–12.0) of fluphenazine, which was continued for an average of 2.6 years (range, 0.01–16.8). The most common side effects were drowsiness (26.1%), weight gain (11.6%), akathisia (8.5%), and acute dystonic reactions (7.0%). Interestingly, none of the patients had tardive dyskinesia.<sup>30</sup>

Aripiprazole was compared to haloperidol in a systemic review that included six randomized controlled studies. The study concluded similar efficacy with significantly less tardive movement disorders with aripiprazole (1.5%) compared to haloperidol (43.5%).<sup>31</sup> Some of the common side effects of aripiprazole include minor symptoms such as nausea, drowsiness, headache, and dizziness in less than 5% of the patients. Thus, it is commonly used in clinical practice for the treatment of tics. Unfortunately, we do not have large-scale multicenter clinical trials to prove this. In a clinical trial, 133 children with TS were randomized in a 1:1:1 ratio to low-dose aripiprazole, high-dose aripiprazole, or placebo for 8 weeks.<sup>32</sup> High-dose aripiprazole was found to be more effective than low-dose aripiprazole, compared to the placebo group. Overall, there was good tolerability and safety profile for tics in children and adolescents.

A newer agent, ecopipam, a D<sub>1</sub> dopamine-receptor antagonist, has shown promising results in the treatment of tics.<sup>33</sup> In a randomized double-blind, placebo-controlled, crossover study, ecopipam showed promising results with a reduction in YGTSS total tic score at 16 days ( $p=0.011$ ) and 30 days ( $p=0.033$ ). The usual side effects of neuroleptics such as weight gain, tardive movement disorders, or laboratory tests or cardiac monitoring, such as ECG, were not seen in this newer agent.<sup>34</sup>

### Dopamine depleters

Tetrabenazine, a monoamine-depleting drug, has been used for the treatment of TS for a long time.<sup>26</sup> In contrast with typical and atypical neuroleptics, tetrabenazine does not produce some of the adverse effects of neuroleptics such as weight gain and tardive dyskinesia. The newer agent, deutetrabenazine, an inhibitor of vesicular monoamine transporter type 2 (VMAT2) depletes presynaptic dopamine and is FDA approved for treatment in Huntington disease and tardive dyskinesia patients. This medication has been studied in an open-label trial of 23 TS patients and there was a reduction in the mean YGTSS score on doses of 18–36 mg/day, and 76% of patients were 'much improved' or 'very much improved' compared with baseline. The reported side effects were headache, fatigue, and irritability.<sup>35</sup>

### Anti-epileptic medications

Topiramate is a commonly used medicine for migraine headaches and epilepsy. There are several studies to evaluate

the efficacy and safety of topiramate in TS. In a meta-analysis, 14 clinical trials were analyzed.<sup>36</sup> The authors concluded that the current evidence is promising but not yet sufficient to support the routine use of topiramate for TS in children due to the low quality of the study designs. As per the AAN guidelines, there is Level B evidence that topiramate should be prescribed for the treatment of tics.

### Botulinum toxin

Botulinum toxin is well-established first-line treatment for several hyperkinetic movement disorders such as dystonia, hemifacial spasm, and blepharospasm. Botulinum toxin can be helpful in simple tics involving one group of muscles, especially for dystonic and clonic tics.<sup>37</sup> In a Cochrane review, one randomized placebo-controlled, double-blind crossover study was included, and the authors concluded that the effect of botulinum toxin in tics is uncertain.<sup>37</sup>

## Deep brain stimulation

In a minority of patients where CBIT and medical management are not able to control disabling tics, deep brain stimulation (DBS) can be considered as an effective treatment option. In 1999, Vandewalle and colleagues<sup>38</sup> reported the first case of DBS with thalamic stimulation in medically refractory TS and found a 90% reduction in tics at 1-year follow-up. Since then, there are many published case reports, case series, and original peer-reviewed articles regarding DBS in TS and tic disorder patients. The ventromedial thalamus has been the preferred target, but more recently the globus pallidus internus (GPI) is gaining popularity. In a randomized double-blind crossover trial, 15 patients received bilateral GPI stimulation, which led to a significant improvement in tic severity with an overall acceptable safety profile.<sup>39</sup> Anteromedial globus pallidus internus DBS is effective in significantly reducing tic severity in patients with refractory TS, without causing any cognitive deficits.<sup>40</sup> In a multinational cohort study, a database of 185 patients with severe TS was reviewed.<sup>41</sup> Patients received DBS implantation in the centromedian thalamic region (93 of 163 [57.1%]), the anterior globus pallidus internus (41 of 163 [25.2%]), the posterior globus pallidus internus (25 of 163 [15.3%]), and the anterior limb of the internal capsule (4 of 163 [2.5%]). The patients had significant improvement in the symptoms on the YTGSS scale at 1 year. The overall adverse event rate was 35.4%, and only 2 patients (1.3%) had intracranial hemorrhage, 5 events of infection (3.2%), and 1 patient (0.6%) required lead exploration. As commonly seen with DBS in other established conditions such as Parkinson's disease, dysarthria and paresthesia were the most common stimulation-induced adverse effects seen in 10 (6.3%) and 12 (8.2%) patients, respectively.<sup>41</sup> The mechanism by which DBS is effective on tics and other symptoms in TS is not yet understood. Based on case series, prospective studies, and a few controlled studies, the average response of 40% improvement on tic severity scales is estimated after DBS

surgery.<sup>37,42</sup> In the future, larger studies to identify the best targets and stimulation settings are required for patients with severe TS.

## Conclusion

Tics and Tourette's syndrome is a common hyperkinetic movement disorder that is seen in the pediatric age group. It is important to have a detailed history regarding the

onset, frequency, and alleviating or exacerbating factors of tics and thorough evaluation for any underlying behavioral symptoms. Management of tics requires collaborative and individualized treatment with patient and family education, clinical assessment, and discussion of treatment options, such as behavioral therapies, and medications and their side effect profiles. Surgical treatment such as DBS is an effective treatment option for a minority of patients who do not respond to behavioral therapy and medications.

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