

Tourette's Syndrome: Old Syndrome, New Insights and New Treatment

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Recognized for over 300 years, Tourette's syndrome was originally ascribed as a rare bizarre psychogenic illness. Because of recent advances in research on Tourette's syndrome, this disorder is not only the rarity once thought, but also a common, biological, genetic disorder with a spectrum of neurobehavioral manifestations that wax and wane during its entire natural course. In addition to standard neuroleptics, much progress in Tourette's syndrome research has widened its pharmacotherapy to include alpha2-adrenergic agonists and atypical neuroleptics as well as behavioral modification, adjustments, and different surgical approaches. Despite a myriad of reports, there are still many unresolved facts, which stimulate research into the underlying mechanisms of this complex neuropsychiatric disorder. We anticipate that continued success of research in this area will lead to molecular insights, identification of vulnerable genes, and eventually novel therapies that can target all aspects of this complex disorder.

Keywords: Tourette's syndrome, Tics, Attention deficit hyperactivity disorder, Obsessive-compulsive disorder

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Tourette's syndrome (TS), once thought to be a psychogenic illness for almost a century, is a neurological disorder named after Georges Gilles de la Tourette (Fig. 1) who described nine patients with childhood-onset tics, accompanied in some by uncontrol-



Fig. 1 George Gilles de la Tourette (1857-1904)

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lable noises and utterances.⁽²⁾ He also noted that these individuals had a variety of comorbid behavior problems, including obsessive-compulsive behaviors (OCB), anxieties and phobias. Tics, the essential component of Tourette's syndrome, refer to abrupt onset, fast, repetitive and brief movements but they can manifest in a variety of forms with different degrees of severity and durations. In fact, no two patients with Tourette's syndrome have the exact same symptoms. Despite advances being made in this area resulting in greater awareness of Tourette's syndrome, many cases are still undiagnosed, or patients' symptoms have been wrongly attributed to allergies, asthma, chronic persistent cough, dermatitis, habits, nervousness and other conditions.⁽³⁾

There are different forms of tics and they are clinical hallmarks of Tourette's syndrome

As mentioned, tics are sudden, repetitive, stereotyped motor movements or phonic productions. They are characterized by their anatomical locations, number, frequency, duration and complexity.⁽⁴⁾ Typically, tics consist of simple or coordinated, repetitive, and sometimes sequential movements, gestures, and utterances that mimic fragments of normal behaviors. Commonly, tics tend to occur spontaneously without provocation by any particular stimulus. However, they



can be precipitated by stress. On the other hand, the effects of relaxation are more variable. While simple tics involve only a single muscle or a group of muscles causing a brief, jerking movement, complex tics are usually longer, more involved, and goal-directed in character. Complex motor tics commonly occur with simple motor tics and are rarely seen in isolation. Clonic tics are simple, jerking movements, for example blinking, shoulder shrugs, head and limb jerking. When the movements are slow, associated with abnormal postures, they are termed dystonic tics, such as torticollis or sustained mouth opening. Tonic tics are isometric contractions of muscles, which are not associated with any overt movements, like tensing of abdominal muscles. Younger patients are often unaware of their simple motor tics. Blocking tics, although uncommon, may occur as a result of prolonged tonic and dystonic tics that interrupt ongoing motor activities, such as speech or any motor activities without alteration of consciousness.⁽⁵⁾ Although tics are usually multifocal and can migrate from one location to another, they most commonly occur in the face, head, and neck regions. The most common presentation is with facial twitching (50-70% of patients).

Motor tics may be accompanied by phonic or vocal symptoms. Theoretically, any noise or sound can be called phonic tics. Similar to simple motor tics, simple phonic tics are fast, meaningless sounds or noises, for example throat clearing, grunting or sniffing. In contrast to complex motor tics, which are common and

tend to occur over time, complex phonic tics, such as phrases or sentences are rare, if ever, present in the absence of simple phonic tics and motor tics of one sort or another. Less than 5% of patients have isolated vocal tics in the absence of motor symptoms. In fact, coprolalia (socially inappropriate words or phrases), which is probably the most recognizable and one of the most distressing symptoms of TS, is actually present in less than half of the patients with TS.⁽³⁾ Other forms of complex phonic tics include repetition of someone else's words or phrases (echolalia) and repetition of one's own last syllables, words, or phrases (palilalia). In addition, some patients may end their vocal tics by including a few socially accepted words, such as cultural bound exclamations.

While some tics, like eye blinking and head jerks, are easily recognized, other forms of tics may be more complex and resemble other hyperkinetic movement disorders, such as dystonia, chorea, and stereotypies (Table 1). The clinical expression of motor tics in an individual patient can be so variable than that seen in other hyperkinetic movement disorders. It is this variability in frequency, duration, amplitude and location of the tics that are often used to differentiate tics from other hyperkinesias. Indeed, the irregular, intermittent occurrence of the tics is in marked contrast to the continuous movements characteristics of tremor, chorea, and tardive dyskinesias. Dystonia refers to sustained muscle cocontractions that frequently cause twisting, repetitive movements and abnormal postures.

Table 1. Differentiation of tics from other hyperkinetic disorders

Types	Characters	Urge	Location	Suppressibility	Phonation
Tics	Sudden repetitive stereotyped movements	Often present with buildup	Face, neck, shoulder	Temporary	Phonic tics
Dystonia	Sustained muscle cocontractions > Abnormal postures	Absent	Focal, segmental, generalized	None	In the form of laryngeal dystonia
Chorea	Irregular, flowing continuous jerky movements	Absent	Frequently in distal limbs and orobuccal region	None	Choreic speech
Myoclonus	Very brief, jerky, unpredictable movements	Absent	Focal, segmental, generalized	None	None
Akathisia	Restlessness	Present but without buildup	Often limbs	Temporary	None
Stereo-typies	Pattern, repetitive continuous, ritualistic movement	Absent	Face, hands	Temporary (occasional)	None



Chorea consists of irregular, unpredictable, brief, jerky movements. The flowing or continuous patterns that move randomly from one part of the body to another help distinguish chorea from tics, which tends to be focal and localized. In addition, the ability to suppress the tics, which is discussed later in this review, helps differentiate tics from these hyperkinetic movements. Stereotypies are involuntary, pattern, repetitive, continuous, coordinated, purposeless or ritualistic movements or postures, which can be differentiated from tics by their lack of premonitory urges and their frequent association with tardive syndromes and developmental disorders, like Rett's syndrome, autism and mental retardation.

Premonitory sensory urges, momentary relief and temporary suppressibility are characteristic features in tics and Tourette's syndrome

The introduction of this review began with the patient's description of sensory and mental stress associated with her tics in order to emphasize these characteristic features in TS. Indeed, many patients with TS report a variety of sensory symptoms, including premonitory urges that incessantly prompt tics and feelings of momentary relief that follow performance of a tic. The urges, described as being besieged by these bodily sensations like an urge to stretch one's shoulder or a need to clear one's throat, tend to localize to discrete anatomical region. Other forms of the urge can be vague sounding like an internal struggle to control them and can be as debilitating as the tics themselves. These urges or sensory happenings create a generalized inner crescendo tension that can only be relieved by performance of a tic. They can be more troublesome than the tics themselves, particularly for some adults who are partially able to resist the tics but are left with distracting urges. More than 90% of patients with TS reported having experienced such urges in one study involving 134 patients.⁽¹⁾ Similarly, 74% of 35 patients with TS reported having a sensation or feeling before tics in a separate study.⁽⁶⁾ These urges are found to be more common in adolescents and adults with more than three years after the onset of the tics and are rare among young children under the age of 10 years with simple tics, such as a forceful eye blinking or a quick head jerk. In addition, they are often located in a small discrete area of the body (hot spots) that can be identified, including shoulder girdles, throat, hands, midline of the stomach, the front of the thighs and the feet (Fig. 2).⁽¹⁾ Less commonly, they are generalized, described as a sense of inner tension.

There are three unique features of tics that help differentiate them from other hyperkinetic movement disorders.⁽⁷⁾ Firstly, as previously mentioned, tics are often preceded by a peculiar sensation and an irresistible urge to move. This sensory-motor relationship is quite unique although can be seen in akathisia, restless legs syndrome, and painful legs and moving toes. However, in akathisia, the feeling of restlessness is relatively constant without crescendo buildup prior to each executing movement. Furthermore, the movements in akathisia seem to be continuous, repetitive and stereotyped. The second unique feature is the ability of the patients to willfully suppress the tics, albeit only temporarily. Voluntary suppression of the tics often leads to build-up tension and eventually even a rebound exacerbation. The typical example is when the patients with tics may be able to conceal the tics during public speaking or when accompanied by strangers, but later release them with exaggerated intensity. Thirdly, in contrast to other common hyperkinesias, tics can persist during all stages of sleep. The recordings of tics during sleep are similar to those observed during wakefulness. These involuntary movements should be differentiated from the more stereo-

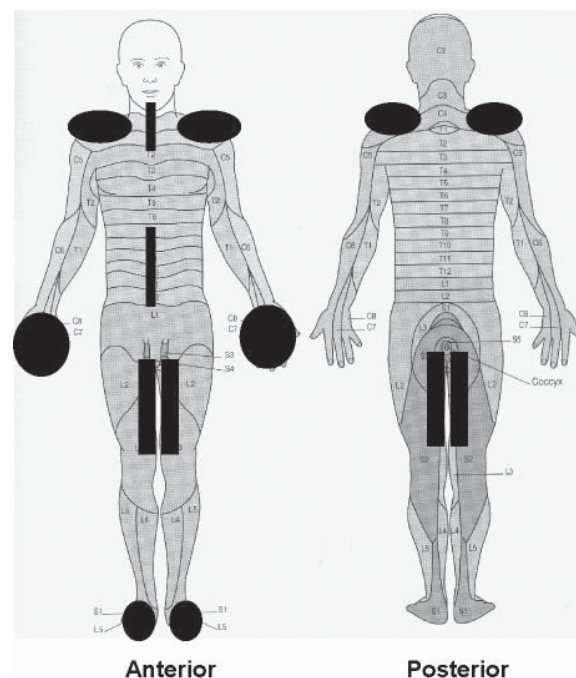


Fig. 2 'Hot spots' areas (shaded black area) of premonitory urges in the palms, shoulders, midline abdomen, inner thighs, feet and throat in patients with Tourette's syndrome



typic, periodic movements in sleep (PLMS, formerly known as nocturnal myoclonus).

How to diagnose Tourette's syndrome?

George Albert Édouard Brutus Gilles de la Tourette (1857-1904), a French neurologist and a student of Jean Martin Charcot at the Salpêtrière hospital in Paris, has gained common recognition through his description of the 'Maladie des Tics'. This complex neuropsychiatric disorder, later known as the 'Tourette's syndrome', nowadays accepted as an entity of movement disorders.

There is no sensitive and specific diagnostic test for Tourette's syndrome and the diagnosis criteria of TS is solely based on the history and observation of tics, often supported by the presence of coexisting behavior disorders, particularly attention-deficit-hyperactivity disorder and obsessive-compulsive disorder, and a family history of similar symptoms. Currently, two classifications are widely used including, the Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-IV)⁽⁸⁾, which is offered by

the American Psychiatric Association, and the Classification of Tic disorder (CTD), developed by the Tourette Syndrome Classification Study Group (Table 2).⁽⁹⁾ Although these two schemes seem to be congruent, clear differences exist. In the DSM-IV criteria (307.23), the disturbances from tics have to cause marked distress or significant impairment in social, occupational, or other areas of functioning in order to diagnose TS while this feature is not a requirement in the CTD criteria. Another difference is the different criterion for age of onset: tic onset before age 18 in DSM-IV, and before age 21 in the CTD criteria. However, most patients (96%) report the onset of their tics in the first decade of life, typically beginning between 3 and 8 years of age. The onset of phonic tics is usually later, with a mean age of onset of 11 years. Therefore, this difference in age of onset is unlikely to make much effect in the diagnosis of TS. Less commonly, coprolalia occurs in less than one-third to half of patients with TS and it usually manifests itself by 15 years of age. When the tics last nearly everyday, for at least 2-4 weeks, but for no longer than 12 months, they are called

Table 2. Diagnostic criteria of Tourette's syndrome (The differences are bold)

	DSM-IV diagnostic criteria	The Tourette Syndrome Classification Study Group
A	Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.	Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B	The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year; and during this period, there was never a tic-free period of more than 3 consecutive months.	The tics occur many times a day, nearly every day, or intermittently throughout a period of more than 1 year.
C	The disturbance causes marked distress or significant impairment in social, occupational, or other areas of functioning.	N/A
D	Onset before age 18	Onset before age 21
E	The disturbance is not caused by the direct physiological effects of a substance (e.g. stimulants) or a general medical condition (e.g. Huntington's chorea or postviral encephalitis).	Involuntary movements and noises can not be explained by other medical conditions.
F	N/A	Motor and/or vocal tics must be witnessed by a reliable examiner directly at some point in the illness or be recorded by videotape or cinematography or tics must be witnessed by a reliable family member or close friend, and description of tics as demonstrated must be accepted by reliable examiner.



transient tic disorder (DSM-IV, 307.21). Often a retrospective diagnosis, transient tic disorder is a common condition of all children with a typical age of onset between 3 and 10 years. Missed diagnosis is probably very common because the symptoms may go unnoticed or disappeared completely by the time of consultation.

Epidemiology and pathophysiology

Once thought to be a rare disorder, the prevalence of TS is estimated to be between 31 and 157 cases per 1000 in children aged 13-14 years.⁽¹⁰⁾ The majority of studies found that approximately 10% of youngsters have tics. Frequency varies by age, sex, source of sample and method of assessment. In addition, many epigenetic factors may play a role in the pathogenesis of TS, reflecting higher likelihood of developing tics or TS in certain groups of children, particularly children with special educational needs and autistic spectrum disorders (Table 3). In general, males are more often affected with TS than females. Typically, the tic symptoms worsen between 7 and 15 years of age, followed by a postpubertal attenuation and adult stabilization. Although the adulthood course of TS is generally stable, with 65% of patients not exhibiting any change in symptomatology over 5 years, the symptoms can wax and wane with 90% of adult patients (age > 20 years) reported to have persistent tics in one long-term outcome study.⁽¹¹⁾

Since the first description by Gilles de la Tourette of possible inheritance in nature, it is generally accepted that TS is at least partially genetically determined. This is supported by studies of monozygotic twins showing an 86% concordance rate with TS, compared with 20% in dizygotic twins and increased rates of chronic tics and transient tics are also observed in the relatives of TS probands. Despite the increasing evidence of inherited nature, no candidate loci have been exactly identified, possibly due to phenotypic variability resulting in inaccurate diagnosis, genetic heterogeneity and influence from other non-genetic factors. Furthermore, the possibility of post-infectious autoimmune mechanism, particularly pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), has been suggested in some cases of TS. Although no abnormalities in neuropathological examination and standard anatomical neuroimaging have been reported, most evidence point to the basal ganglia dysfunction, particularly the caudate nucleus and the inferior prefrontal cortex, in the pathogenesis of TS. Functional MRI studies reported decreased neuronal activity during periods of suppression in the globus pallidus interna, putamen and the thalamus and increased activity in the prefrontal, parietal, temporal areas normally involved in the inhibition of unwanted pulses. Furthermore, positron emission tomography have demonstrated increased density of presynaptic dopamine transporter and the postsynap-

Table 3. Possible risk factors of Tourette's syndrome⁽¹⁵⁾

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- 1) Genetic vulnerability
 - 2) Gestational and perinatal risk factors
 - Severe nausea and vomiting during the first trimester
 - Severe psychological stress of the mother during pregnancy
 - Maternal use during pregnancy of coffee (more than 2 cups a day), cigarettes (more than ten a day), or alcohol (fewer than two drinks a day)
 - Identical twins with a lower birthweight
 - Low-birthweight children with evidence of parenchymal lesions, ventricular enlargement or both
 - Transient hypoxia or ischemia during birth (labor > 24 hours), use of forceps, nuchal cord, evidence of fetal distress
 - Low Apgar scores
 - 3) Severe psychosocial trauma, recurrent daily stresses, or extreme emotional excitement
 - 4) Recurrent streptococcal infections with post-infectious autoimmune response
 - 5) Drug abuse
 - Exposure to androgenic drugs
 - Chronic intermittent use of cocaine and other psychostimulants
 - 6) Co-existing medical or psychiatric disorders
 - Hyperkinetic disorders
 - Learning disabilities
 - Depression
 - Manic depression
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aggressiveness, antisocial and oppositional behavior.

Treatment options in Tourette's syndrome and associated disorders

Foremost in the treatment of TS is the education of the patient and the family. An explanation of the symptoms, including associated behavior disorders, allows for an appreciation that these are not entirely voluntary. Often, patients will suppress the tics throughout most of the day, only to exhibit many tics when he/she returns home from school. Therefore, the family should understand that it is necessary for the person to 'release' the tics. In addition, particular times of the year may be more stressful than others, for example starting school or close to the examination period. Education of teachers or coworkers is also important. National associations and local support groups, such as the Tourette Syndrome Association (www.tsa-usa.org), the Movement Disorders Society (www.movementdisorders.org), and Worldwide Education and Awareness for Movement Disorders (www.wemove.org), serve as a valuable source for patients, families and healthcare professionals. A variety of psychological therapies have been used, particularly when associated with OCD as an adjunct to medications. While some techniques have been shown to be effective, for example assertiveness training, self-monitoring and cognitive therapy, relaxation therapy has not been proven to be useful in the treatment of tics. Most patients with mild TS who have made a good adaptation in their lives may not require any medications. On the other hand, pharmacotherapy should be considered once it is determined that tics are functionally disabling and not remediable to psychosocial interventions. It is important to understand that the goal of treatment should not be to completely eliminate all tics, but to achieve tolerable suppression.

Pharmacotherapy is, at present, the mainstay of treatment of motor and vocal symptoms of TS, as well as some of the associated behaviors. The treatment can be complex and combination strategies are often required according to which symptoms are being primarily targeted. Relatively few studies exist and the controlled trials have been conducted on small numbers of patients. In addition, tic-suppressant medications generally need several weeks to achieve their full effects. Therefore, it is often difficult to distinguish response to a drug from spontaneous improvement of symptoms. Generally, it is best to avoid beginning or increasing drugs as soon as exacerbation begins. Currently, two classes of drugs are most widely used to

control tics associated with TS: α_2 adrenergic agonists and neuroleptics. Dopamine receptor-blocking drugs (DRBAs, neuroleptics) have been found to be the most effective agent in numerous trials. Haloperidol (Haldol[®]) and pimozide (Orap[®]) are the only DRBAs actually approved by the US. Food and Drug Administration (FDA) for the management of TS. Although haloperidol, primarily D2 receptor blocker, appears to be the most widely used agent, it has been shown to produce more side effects, including sedation, weight gain, depression, school phobia, parkinsonism, and tardive dyskinesia when compared to other neuroleptics. Therefore, some physicians prefer to use fluphenazine, risperidone, molindone, and tiapride.³ The starting dose of haloperidol is usually 0.25 mg at bedtime, increasing as necessary to 2 mg per day or less, given at bedtime. Pimozide can prolong QT interval so patients treated with this drug must undergo an electrocardiographic test before initiation of therapy, 3 months later and annually thereafter. The starting dose of pimozide is 1 mg per day. For the patient with mild or moderate TS, one approach is to use an α -agonist as the first-line agent. Clonidine can be initiated at 0.05 mg at bedtime, and the dose can be increased by 0.05 mg every few days until satisfactory control of tics is achieved or unacceptable side effects are encountered. Most patients respond well to 0.1 mg three times per day, given before and after school and at bedtime. Sedation is a limiting factor in children taking clonidine. Transdermal clonidine can be considered as an alternative although side effects of skin irritation and the patch falling off are well recognized. Guanfacine (Tenex[®]) is a new generation of α -agonist that has less sedation and can be given once daily. The starting dose of guanfacine is 0.5 mg at bedtime and gradually increased to a maximum dosage of 4 mg. Because of the high risk of tardive dyskinesia associated with typical neuroleptics, atypical agents, including clozapine (Clozaril[®]), olanzapine (Zyprexa[®]) and quetiapine (Seroquel[®]) have been tried although it is unclear if they are effective anti-tic agents. Ziprasidone (Geodon[®]) was found in one study to diminish the tic severity by 35%. Some physicians prefer atypical antipsychotics as second-line tic-suppressants after the α -agonists but before typical neuroleptics due to side effect profiles. In patients with severe tics, antipsychotics may be considered as the first-line treatment rather than an α -agonist due to rapid response. Tetrabenazine (not available in Thailand), a monoamine depletor and dopamine receptor blocker, is a powerful anti-tic medication and has an advantage



over conventional neuroleptic in that it has not been reported to cause tardive dyskinesia.

The efficacy of D2 antagonist, like some DRBAs, can be understood theoretically in terms of the standard model of basal ganglia circuitry. Therefore, blocking the postsynaptic D2 receptor in the striatum in patients with TS should decrease thalamic release of glutamate into cortex, resulting in tic improvement and an agonist at the postsynaptic striatal D1 and D2 receptors should theoretically worsen tics. In contrast to the proposed mechanism, dopamine agonists at low doses, including pergolide and ropinirole has been found to be effective in the treatment of TS in a double-blind, randomized and a pilot studies respectively. The improvement may be related to the down-regulation of the dopamine release from low-dose presynaptic dopamine receptor stimulation. In addition to dopamine modulating agents and alpha-agonists, other drugs found to be effective in the treatment of tics include clonazepam, cannabinoids, nicotine patches, baclofen, and anticonvulsants, but none of these medications have been studied in well-designed, placebo-controlled trials. Focal motor and vocal tics may be successfully managed with botulinum toxin injections in the affected muscles. Such focal chemodenervation ameliorates not only the involuntary movements, but also the premonitory urges.⁽¹³⁾ Lastly, surgical treatment of TS of various procedures, varying from ablative surgery to thalamic deep brain stimulation (DBS), has been performed in intractable cases with inconsistent results and it is at present considered experimental.

The most commonly accepted treatment for ADHD involves the use of stimulants, particularly methylphenidate (Ritalin®) and dexamphetamine (Dexedrine®). However, it has previously been recommended that the use of stimulants be avoided in the treatment of ADHD in children with tics, because of the concern that tics can worsen with their use. The study, conducted by the Tourette's Syndrome Study Group, clearly demonstrated that significant improvement in ADHD symptoms occurred in subjects treated with clonidine and methylphenidate individually, or with the combination of the two giving the greatest benefits.⁽¹⁴⁾ In addition, the use of stimulants had no statistically significant effects on tic severity. Thus, the use of stimulants is not contraindicated in patients with TS and the worsening of the tics is probably not a direct pharmacological effect, rather reflects natural fluctuations in tic severity that occurs over time. Aside from behavior therapy, selective serotonin re-uptake

inhibitors (SSRIs) are a mainstay of treatment of OCD. Although there have been no head-to-head comparative trials, fluoxetine, sertraline and fluvoxamine are among the best tolerated SSRIs. In addition to the benefits in relieving symptoms of OCD, SSRIs have been shown to be effective in the management of anxiety, phobias, and the improvement of the urge.

Tourette's syndrome has a life-long course. Once considered to be a psychogenic disorder, present ideas about TS suggest the involvement of many neurotransmitters in the basal ganglia and connected structures. Tics in TS may therefore originate from an abnormal basal ganglia discharge that leads to thalamo-cortical activity, thus causing involuntary movements. Once thought to be a rare disorder, newer studies suggest a higher prevalence in both normal and autistic-spectrum populations. Unfortunately, many cases with TS are still undiagnosed, partly due to the lack of awareness of the disorder and its comorbid conditions. The difficulty does not limit to only the diagnosis, but also the therapeutic decisions. The treatment should not be restricted to only pharmacological intervention, but also education and behavior therapy. In fact, no two patients with TS exhibit the exact same symptoms and need the exact same treatment. The management should be individualized, involving patients, parents, school teachers and physicians. Thanks to the progress in research on Tourette's syndrome, treatment strategies for TS and its comorbidities are improving with newer agents providing significant relief with fewer side effects. Furthermore, the authors are optimistic that discoveries of the new diagnostic facilities and treatment will dramatically increase our understanding of this unique, complex and fascinating disorder.

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โรค Tourette: จากช่วงของการค้นพบจนถึงความรู้และการรักษาในปัจจุบัน

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โรค Tourette ตั้งแต่ถูกค้นพบมากกว่า 300 ปี ในช่วงแรกยังถูกเข้าใจว่าเป็นโรคทางจิตเวชศาสตร์ที่พบได้น้อยมาก แต่เนื่องจากความก้าวหน้าทางการวิจัยในโรค Tourette ทำให้ความเข้าใจของโรค Tourette ในปัจจุบัน ต่างจากสมัยก่อนซึ่ง เป็นโรคที่พบได้บ่อย และมีความซับซ้อนที่เกี่ยวข้องกับระบบประสาท พันธุกรรม และจิตวิทยา วิธีการรักษาโรค Tourette ในปัจจุบันนี้ก็มีมากขึ้นจากสมัยก่อน ซึ่งนอกเหนือจากการรักษาด้วยยาในกลุ่ม standard neuroleptics แล้ว การรักษายังได้รวมไปถึงยาใหม่ในกลุ่ม alpha2-adrenergic agonists, atypical neuroleptics, behavioral modifications, adjustments และการผ่าตัดหลายๆ แบบ ถึงแม้ว่าสาเหตุของโรคยังไม่เป็นที่ทราบโดยแท้จริง แต่ด้วยความก้าวหน้าและผลงานวิจัย ในโรค Tourette ที่มีออกมาอย่างสม่ำเสมอ ทำให้ผู้เขียนหวังว่าสาเหตุที่แท้จริงของโรค Tourette คงจะเป็นที่ทราบในอนาคตอันใกล้ รวมไปถึงการรักษาที่ครอบคลุมไปถึงอาการอันหลากหลาย และซับซ้อนในโรคนี้