# Current Insights in Tourette Syndrome, Treatment Options and Future Perspectives

Bachelor Thesis

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## Abstract

Tourette Syndrome (TS) is a neurological disorder causing tic behaviours. Much is unknown about Tourette and comorbidities are highly prevalent and strongly impairing. Current therapies rely largely on trial and error and many patients are not receiving optimal treatment. Standard treatments often include medication and might not benefit patients greatly. Personalized therapy and guidance could alleviate the problems resulting from Tourette. Inducing social acceptance and administering proper training should be tried before any invasive therapies are performed.

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## Introduction

Tourette syndrome (TS) or simply Tourette is a neurodevelopmental disorder in which individuals perform involuntary behaviours called tics. Tourette is fairly unknown and misunderstood in today's society. One of the reasons for this is the great variety in Tourette phenotypes between individuals, where some have very obvious tics others can experience very subtle but disturbing symptoms. This became obvious to me from a young age since Tourette has been present in my family for several generations that I know of. When people met my father for the first time I always had to explain the disease to them. His tics were quite a strong presence and could be startling to people unfamiliar with the disease. My brother on the other hand experienced lighter tics that, in most cases only people close to him noticed. Several years after his diagnosis, I am not able to recognise the tics themselves in his behaviour and I am not sure whether he experiences any tics at all anymore.

Both my father and brother have taken medication for their Tourette at a certain moment and both have undergone a variety of behavioural treatments. However these treatments and medications most often turned out to have adverse effects outweighing the benefits or there were no effects whatsoever. This seemed like a great example to show the difficulty in treating the symptoms of Tourette as there are many different individuals with many different forms of the disease which suggests that researching personalized treatments for Tourette could improve the course of this disorder. Tourette can be a highly impairing disorder, affecting individuals in a great manner throughout their life. For this reason, it is important that advances are made in the fields of neurobiology and psychology to improve the quality of life in patients. Eventually, the ideal solution is discovering neuropathological changes in brain structures or disturbances in neurological pathways possibly leading to concrete solutions for curing Tourette. This overview article will try to contribute to the understanding of Tourette and it's complexities by clarifying the current state of Tourette.

The goal of this paper is to give an overview of Tourette syndrome, it's comorbidities and the current state of therapy, since a lot of aspects of Tourette patients are misunderstood or even mistreated. With this article I want to educate people about Tourette and prevent patients suffering from this disorder to be overlooked or mistreated. With this thesis I will try to show that nowadays, patients often are not receiving optimal treatment for their symptoms and might benefit from non-conventional or combined therapies. Lastly, I will try to show the importance of developing new ways of treating the symptoms or even the disease itself.

To achieve this, the main question that should be answered is 'What is the current state of therapy for Tourette patients and how can Tourette treatment be optimized to best fit individuals?'. This thesis is divided in several parts discussing subjects such as the neurobiology of Tourette, it's comorbidities, Tourette treatments and problems that have emerged in Tourette treatment. There is an abundance of interesting research fields regarding Tourette including but not limited to the role of the immune system, prenatal risk factors and even cerebral endocannabinoids[1]. This thesis however will focus on the most advanced developments and treatments since there is simply too much information to include every subject. The research deemed most important will be covered to give an overview of Tourette syndrome.

## What is Tourette syndrome?

Tourette syndrome is a neuropsychiatric disease named after the French neurologist George Gilles de la Tourette. Tourette is characterised by multiple motor tics and at least one vocal tic persisting for a minimum of 1 year[2]. A tic is classified as an involuntary, sudden, repetitive behaviour[3] and is often preceded by an 'urge' in individuals with Tourette. To be diagnosed with Tourette the first tics must have occurred before an individual reaches age 18 and must not be the result of an underlying medical condition or be caused by any form of medication[4,5]. Tics in Tourette can manifest themselves in a variety of ways and fluctuate throughout an individual's life[5] . The tics in individuals suffering from Tourette often improve with age and about one third of adults with Tourette does not experience any tics at all[5]. Both the motor and vocal tics in Tourette can be classified into two different subgroups, simple tics and complex tics. Simple motor tics include behaviours like blinking, grimacing or shoulder shrugging, simple vocal tics can for example occur as throat clearing, sniffing or grunting[6]. Complex motor tics include tapping objects, clapping or making obscene gestures. Echolalia (repeating another speakers words), palilalia (repeating your own spoken words) and coprolalia (uttering socially unacceptable words) are examples of complex vocal tics[6]. The intensity of tics is strongly affected by environmental factors and the state of an individual. Stress and anxiety can exacerbate the tic severity while focusing on specific tasks can reduce the tic intensity[6].

Studies performed in the previous century mostly found that Tourette was a rare disorder occurring in an estimated 5 out of 10,000 school age children[7]. However more recent studies are finding that Tourette prevalence is a lot higher in this group, most studies estimate a prevalence of 0,3% to 0,9% in school age children[8,9]. Large differences have been found regarding prevalence in different sexes. The male to female ratio of Tourette patients has been found to be approximately 4:1[9,10]. In adults the male to female ratio becomes more or less equal with a much lower prevalence of around 0,077%[11]. There is no consensus as to why these gender differences exist.

Tourette disease is assumed to be highly familial. Studies quantifying the heritability in large cohorts give an estimated heritability of 55-56%[12,13]. This strong degree of heritability suggests the presence of genetic factors contributing to the development of Tourette. While no concrete genes have been found that would increase the risk of developing Tourette, recent findings suggest important roles of some genetic factors[14]. One important example is the SLITRK, a gene that has been implicated in several studies to be a susceptibility gene for Tourette[15,16]. The last several years more genetic factors or relevant loci are found to be implicated in Tourette. Identifying these genes can increase the understanding of Tourette development and its origins.

## The current state of Tourette syndrome

Very little is known about Tourette, there are some hypotheses as to the origin of the disorder or factors affecting it's development. Maternal smoking during pregnancy has been shown to increase the chance of developing Tourette by twofold[17]. Other prenatal stressors have been hypothesized to exert similar effects on children[18]. Some studies even state that immune mechanisms affect neural development possibly inducing Tourette[19]. However there have not been any significant breakthroughs in these fields leading to a clear origin of Tourette.

There are theories about the pathways and brain areas involved in Tourette. It is widely accepted that the basal ganglia and the cortico-striatal thalamic pathway are involved but these areas are so broad that they are involved in a majority of brain processes. Other than these brain structures, dopaminergic and serotonergic pathways in the brain are involved in tic behaviour and Tourette[20]. These neurotransmitters have an enormous variety of effects and identifying the right pathway to determine the pathology of Tourette will be a challenge for the future.

**Table 1. Diagnostic Criteria for Tourette's Syndrome.***

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|---|
| Both multiple motor tics and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. |
| The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 3 consecutive months. |
| The onset is before 18 years of age. |
| The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis). |

* Criteria are from the *Diagnostic and Statistical Manual of Psychiatry*, 4th edition.[1]

*Figure 1. Diagnostic criteria for Tourette Syndrome[5]*

Even more worrying than the lack of knowledge concerning Tourette neurobiology is the fact that Tourette does not even have a clear symptomology, apart from the diagnostic criteria. There are many comorbidities affecting Tourette patients causing a wide range of Tourette symptoms. This can result in difficulties for physicians because they need to evaluate each case individually and search for the best approach. A large aspect of the current system is to find a universal treatment, this is not doable in Tourette and any effort to achieve this could prove to be useless. A universal treatment will lead to a lack of distinction between patients and where some get beneficial treatments, the situation of others might deteriorate.

Summarizing, our inability to treat Tourette remains a significant problem. Because very little is known let alone understood, physicians and therapists are not able to recognise, diagnose and treat every Tourette patient in a way that sufficiently reduces their impairment. Tourette is not a life threatening disease and in many cases patients are quite able to handle their symptoms. It can however strongly disrupt a 'normal' life and there might be underlying problems we have not figured out yet. Therefore it must be stated that Tourette treatment at the moment is not satisfying the demand for help and steps have to be taken to improve this.

## Tourette syndrome neurobiology

The neuroanatomy of Tourette has proven to be a very complex subject and many studies have been performed to determine the neurobiological changes in Tourette patients. At the moment there are no concrete findings as to differences in brain anatomy. Over the years however, many research groups have found brain areas that are very probably involved in the pathology of Tourette. One of the most consistent findings concerns the involvement of a disturbance in the basal ganglia in Tourette[21,22]. The basal ganglia consist of several components and are among other things involved in motor control and movement[21]. Most studies regarding volumetric changes deliver varying results but an overall trend of volume reduction seems to be present, most notably in the caudate nucleus[21,23,24].

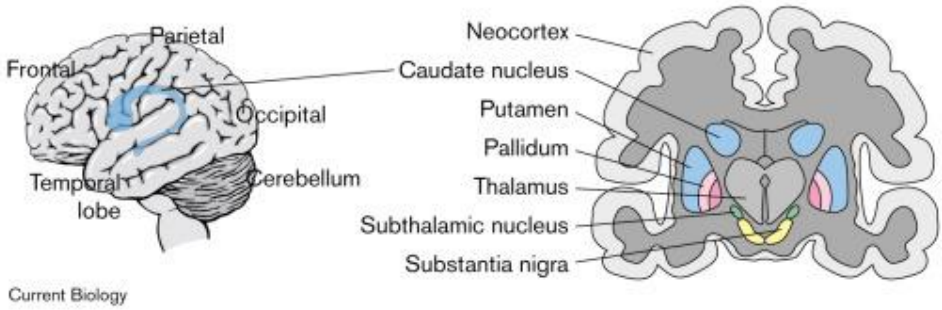


*Figure 2. Neuroanatomy of the basal ganglia, thalamus and neocortex, structures involved in Tourette neurobiology[29]*

These volumetric changes in the basal ganglia are hypothesized to affect Tourette pathology via the cortico-basal ganglia-thalamic-cortical pathway influencing the thalamus and parts of the cortex[25]. This can be supported by the finding of cortical thinning at several sites by research groups[26,27,28]. What the precise implications of all these and other less significant findings are is still unknown, the importance of the cortico-basal ganglia-thalamic-cortical pathway however seems significant.

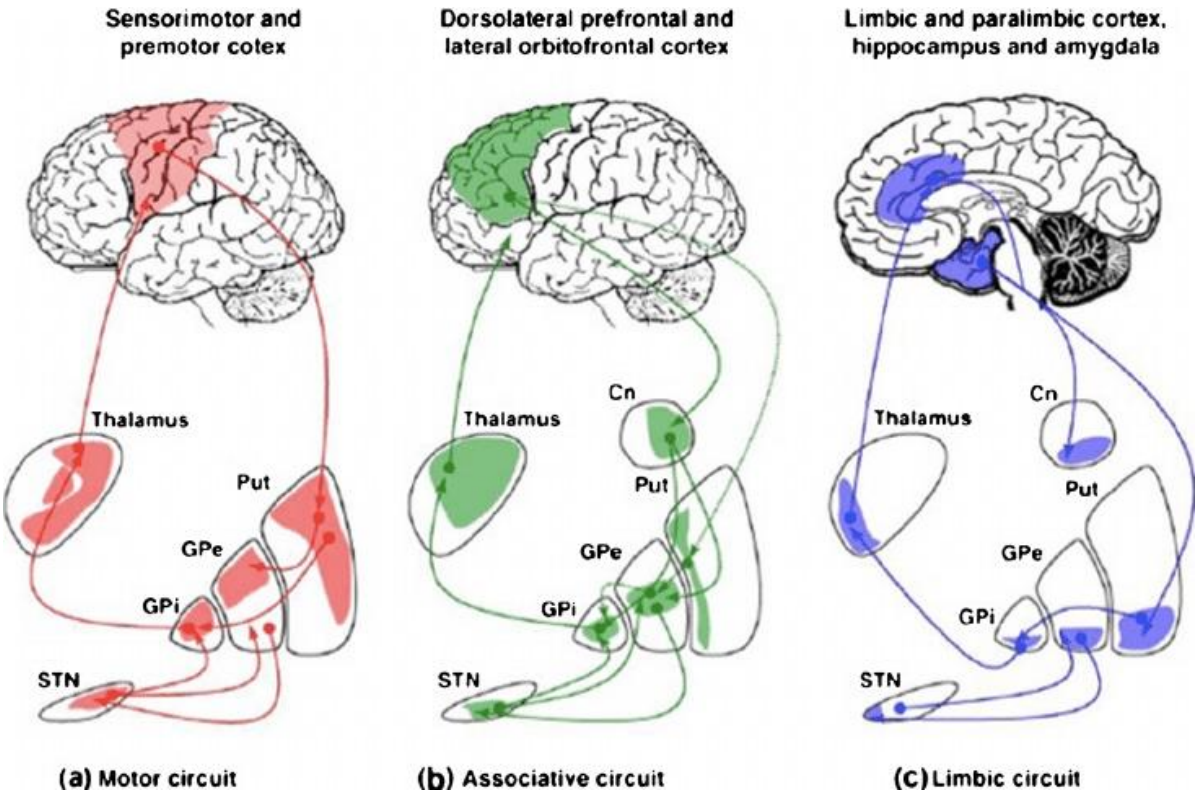


*Figure 3. Cortico-striato-thalamocortical loops thought to be strongly involved in Tourette neuropathology[30]*

Other than structural changes in the brain, Tourette has for a long time been thought to involve disturbances in dopamine balance[31,32]. Dopamine hyperinnervation has been hypothesized to explain findings in Tourette patients resulting in increased tonic and phasic dopamine[33]. Computational models have, in turn been shown to explain many Tourette characteristics[34]. Other theories regarding the role of dopamine in Tourette include: supersensitive dopamine receptors, overactive dopamine transporters and presynaptic dysfunction in dopamine neurons[33]. All these theories could be used to explain the efficiency of medications that reduce dopamine signalling. There are however different views regarding these theories with some studies confirming these theories and others questioning them[35].

A dopaminergic pathology hypothesis for Tourette is strengthened by the high prevalence of comorbid ADHD. The hypotheses involving dopamine dysfunction in ADHD suggest a large overlap with Tourette neurobiology. Similar pathways are thought to be involved in these disorders and dopamine is a key factor in both ADHD and Tourette[36,37].

Similar to dopamine, research has postulated the theory that serotonergic pathways are involved in Tourette as well[38]. While this idea is less developed than dopaminergic hypotheses, there is quite some evidence supporting serotonergic dysfunction in Tourette patients[38,39]. Similar to ADHD associated with dopamine dysfunction, OCD is strongly associated with serotonin dysfunction[40] and suggests a link between Tourette and serotonin. It should be considered that the complex interactions between dopamine and serotonin could explain the involvement of one as a result of the other and there are no overwhelming conclusions involving either one of these neurotransmitters. Similarly, underlying mechanisms or comorbidities might influence the balance between serotonin and dopamine and no decisive conclusion can be drawn at the moment.

## Tourette syndrome comorbidity

To be diagnosed with Tourette, an individual needs to display motor and vocal tics as mentioned earlier[5,41]. However, patients with Tourette often suffer from comorbid disorders affecting their lives more than the tics themselves. Distinguishing the different comorbidities is difficult since individuals often suffer from a specific combination of various neuropsychological diseases.

One of the comorbidities with a high prevalence in Tourette patients is Attention-Deficit Hyperactivity Disorder or ADHD. Individuals suffering from ADHD experience symptoms like distractibility, hyperactivity and impulsivity with the possibility of developing emotional liability and a short attention span[42]. The percentage of Tourette patients with comorbid ADHD has been found to be about 55% in large studies (more than 1000) regarding subjects with Tourette[10,43]. The prevalence of comorbid ADHD was found to be higher in males than in females with 58,5% and 42,3% occurrence respectively[43].

While both the neurobiological pathways for ADHD and Tourette are relatively unknown, many studies implicate an important role of the basal ganglia thalamocortical pathways[44,45,46]. While many brain areas and neurotransmitter balances are influenced by pathologies such as Tourette and ADHD, a key change seems to be cortical thinning in the prefrontal striatal systems. This decrease in volume of the prefrontal cortex is hypothesized to be associated with less inhibition of impulsive and socially 'unacceptable' behaviours[47]. It might be the case that tics in Tourette originate in a similar manner and are affected by this phenomenon in ADHD.

The second most occurring comorbidity is Obsessive Compulsive Disorder or OCD. The prevalence of this disorder has been found to be around 50%[43,49]. OCD was found to be occurring more often in female subjects with a prevalence of 57,1% versus a prevalence of 47,5% in male subjects[43]. OCD is an anxiety based disorder characterized by symptoms such as unwanted and obsessive thoughts and repetitive behaviours a patient feels driven to perform[50,51]. Since tics in Tourette and compulsive behaviours in OCD are very similar, it is often difficult to distinguish one from the other. While the age of onset and familial pathologies can be an indication of the diagnosis that fits best, studies have found differences in the compulsive behaviours of the disorders. Tics in Tourette patients are more often associated with a mental or bodily sensations that build up and give individuals the urge to release this 'energy' to relieve the feeling of incompleteness[52]. Compulsive behaviours in OCD are more often anxiety based and can often be associated with obsessions such as hand washing or checking. Individuals suffering from OCD know their behaviours are irrational and do not enjoy performing them but rather give an escape from the built up distress caused by certain stimuli[51]. Several dopaminergic and serotonergic cortico-thalamic pathways are involved in both Tourette and OCD[40]. Therefore one is often concomitant to the other resulting in a spectrum of tics and obsessive compulsive behaviours[43,49].

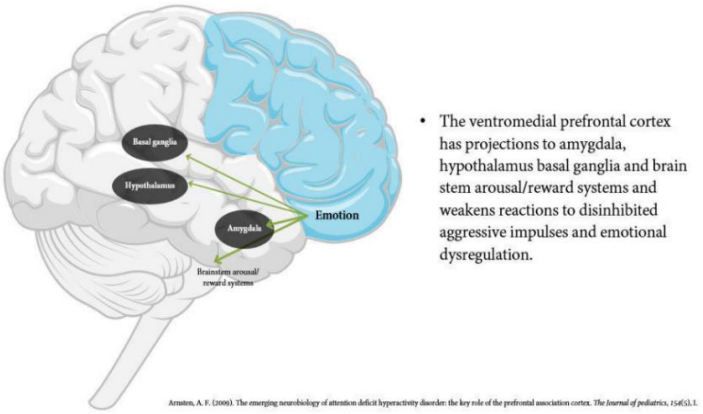


*Figure 4. A decreased inhibition of emotions and impulsive behaviours might be the results of prefrontal cortical thinning[48]*

Tourette patients reaching adolescence or adulthood often experience a decline in tic severity or tic frequency[5] while the increased prevalence of major depression and depressive symptoms only becomes significant in adolescents and adults[53]. Tourette patients have a significantly higher prevalence of major depression during or close to adulthood (26,1%), mood disorders (29,8%) and anxiety disorders (36,1%) as found in a large study consisting of 1374 Tourette patients and 1142 unaffected family members[43].

Both Tourette and depressive symptoms have been found to be associated with neural pathway disturbances. The mechanism of development for both disorders is complex and features a large number of factors. Serotonergic and dopaminergic pathways seem to be the most important neurotransmitters in the development of these disorders[54,55]. The hypothesis could be made that these overlapping systems cause the increased prevalence of depression like disorders in Tourette patients. There are however other possible explanations. OCD is an often occurring comorbidity and depression prevalence is significantly higher (13% - 75%) in individuals suffering from OCD[56]. The same phenomenon is present in individuals with comorbid ADHD although depression prevalence is lower in this subgroup[56]. Another factor hypothesized to influence the development of depressive symptoms is the response to social difficulties as a result of Tourette. Bullying, insecurity and social exclusion could be key contributors to the development of depression like disorders[57,58]. Lastly, depression like symptoms could be the result of treatment with antipsychotics. Many of the approved antipsychotic drugs can induce depression like symptoms and these are often administered in Tourette therapy[56]. The most logical explanation for increased depression prevalence is that the role of depression as a comorbidity is relatively unknown and probably originates from a variety of factors including social stress and comorbid disorders.

Some studies have suggested that Tourette patients have a significantly higher prevalence of comorbid autism spectrum disorder (ASD)[59,60,61,62]. While their neuropathology and symptomology have much in common[63], there are not a lot of concrete prevalence numbers from large studies. It is possible that Tourette patients do not have an increased risk for developing ASD and that Tourette symptoms are misdiagnosed as comorbid ASD (especially with comorbid ADHD). Similarly, it could be the case that tics in autistic individuals are misread as symptoms of ASD. On the other hand Tourette patients with comorbid ASD could be diagnosed as simply having an autistic disorder since tics are not uncommon in individuals diagnosed with autism[59,64]. No concrete statements can be made for there is too much uncertainty regarding the comorbidity of these disorders. At the moment it seems evident that ASD and Tourette have a lot of overlap and strongly influence each other. The two disorders are however very hard to classify while little is known about either of them.

It should be stated that not all Tourette patients with additional diagnoses that fit the disorder have comorbidities. A young boy that has been diagnosed with Tourette and comorbid ADHD might simply display strong tic behaviour as a result of his ADHD. Similarly a Tourette patient's ADHD might influence his mental health affecting his mood, resulting in two comorbidities that can be diagnosed. These disorders are relatively unknown and follow complex pathways and systems that strongly influence each other. Therefore in many cases there is no single diagnosis and it might benefit patients if experts treat them while keeping an open mind.

## Tourette syndrome treatment

Since every Tourette patient is unique, there is no consensus on the treatment of an individual's symptoms. While some patients have a very high tic severity and no comorbidities others can have little tic discomfort but extreme forms of OCD or ADHD decreasing their quality of life. These therapies vary in a large way and while some could be standard procedure in Tourette treatment, others should be used only in very specific cases with a very low quality of life.

At the moment several treatments exist for Tourette symptoms some focusing on tics and others on comorbidities. Individuals experiencing severe motor or phonic tics could benefit from local Botulinum Toxin (Botox) injections repressing the muscles performing the repetitive behaviour[65,66,67]. These Botox injections block acetylcholine release locally at the neuromuscular junction causing muscle paralysis[68]. This way, an individual is unable to execute the tic, decreasing tic frequency. Botox injections can be administered into an individual's hand, finger, face or even vocal cords to reduce tics[65,66]. These injections work for local tics and become increasingly difficult with behaviours affecting larger parts of the body. Botox injections are not only able to reduce the amount of expressed tics but also the premonitory sensations preceding them[65] making it a promising tool for the treatment of Tourette.

The least invasive way to help Tourette patients cope with their tics concerns forms of behavioural therapy. In patients that develop Tourette symptoms (mostly children) the therapy that is applied relies on the education of a patient and their environment, this often solves a lot of discomfort but does not apply to the symptoms themselves. Some patients might not have severe enough tics to be interested in medication or forms of medical intervention but these individuals still live with the problems the disease causes for them. Patients suffering from more severe Tourette symptoms might also benefit from a combination of medical treatment in combination with behavioural training.

To decrease the severity of tics in Tourette patients a promising form of treatment has been developed called Comprehensive Behavioural Intervention for Tics or CBIT. CBIT focuses on alleviating tics by consisting of three components: Training the patient to be more aware of his or her tics and the urge to tic, training patients to do competing behaviour when they feel the urge to tic and making changes to day to day activities in ways that can be helpful in reducing tics[69].

By making Tourette patients aware of their tics and their stimuli and having them perform a competing behaviour they break a negative reinforcement cycle. This negative cycle is created by the relief of performing a certain tic, repeating the tic alleviates the unpleasant feeling of the premonitory urge which in itself promotes an individual to perform the tic when the urge resurges after some time[70]. By replacing the original tic with a less intense behaviour that does alleviate the premonitory urge to a certain degree, this cycle is broken or at least disrupted, positively affecting tic behaviour[71]. This is different than tic suppression since this habit reversal training is focused on decreasing tic severity instead of learning the ability to supress the behaviour in socially awkward situations without decreasing the premonitory urge.

A study concerning the effect of CBIT on Tourette patients aged 9 to 17 found significant decreases in tic severity measured by the Yale Global Tic Severity Scale (YGTSS). A 7.6 point decrease was found in the CBIT group with only a 3.5 point decrease on the YGTSS in the control group that did not receive any structured training and thus experienced the basic form of therapy most children with Tourette receive nowadays[71]. Another study with 438 participants found no significant difference between their CBIT treated individuals and meta-analyses of earlier studies in which Tourette patients were treated with antipsychotic medications[72].

One of the most invasive therapies for Tourette and other neuropsychological disorders like Parkinson's disease is Deep Brain Stimulation (DBS). DBS is a surgical procedure in which electrodes are inserted into the brain resulting in electrical stimulation of targeted brain areas[73].

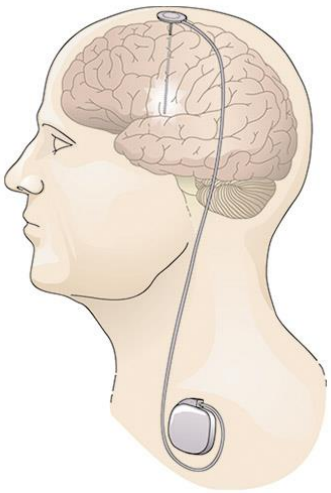

*Figure 5. A model showing the placement of the electrode in DBS[74]*

DBS is already an FDA approved therapy for severe cases of Parkinson's Disease, essential tremor, dystonia, OCD[75] and epilepsy[76]. However, patients suffering from these conditions are examined individually and not every patient is allowed to undergo this procedure[77]. DBS is being researched as a therapy for the symptoms of Tourette as well as major depression, multiple sclerosis, chronic pain and several other disorders and diseases[77]. It is however a very intensive treatment and comes with adverse effects such as seizures, bleeding in the brain, strokes and more, while delivering no certainty in treatment benefits[77].

In Tourette patients, large overview studies (n≈150) found that DBS significantly improved tics and obsessive-compulsive behaviours over time with little to no variation between brain areas targeted[73,75,78]. The areas targeted in DBS concerned the centromedian thalamic regions, different regions in the globus pallidus, the nucleus accumbens and the subthalamic nucleus[73,75,78]. Some individuals experienced targeting of several brain areas but this was mostly due to the first targets not giving any result. After the treatment of these individuals the symptoms of Tourette (only tics and obsessive-compulsive behaviours) decreased significantly. On the long term these benefits are less promising, a study of 18 individuals found that three out of four subjects experienced less than promising results after three to four months of DBS treatment resulting in the need to frequently reprogram the DBS system[79]. This shows the fragility of the DBS treatment in Tourette patients.

The benefits of DBS treatment however should be weighed against the possibility of severe adverse effects. The positive effects might not be as present in an individual as was found in studies which makes it difficult to consider. A study of six individuals found a 37% improvement of tics on the YGTSS which is substantial. Their six subjects reported significant adverse effects such as lowered energy levels and subjective gaze disturbances. One subject suffering from comorbidities such as depression and self-injurious behaviours experienced psychogenic paroxysmal hypertonia, mutism and disturbances of consciousness[80]. This subject had to be removed from the trial and shows the risk involved in DBS treatment in patients suffering from a spectrum of mental illnesses or Tourette comorbidities. In another study less extreme cases adverse effects like dysarthria (10 out of 158 subjects), paresthesias (13 out of 158), infections (4 out of 158) and a variety of stimulation related adverse effects varying greatly between individuals (48 out of 158) were reported[73].

When behavioural therapy or local tic intervention does not improve the quality of life sufficiently, Tourette patients can decide with a skilled physician that medication might be helpful. It should however be taken into account that there exists a high variability between Tourette patients and pharmacotherapy that is beneficial for one individual might only negatively influence other patients. Antipsychotics are often the first type of medication that is administered in Tourette patients experiencing severe tics[81]. Antipsychotics are a group of drugs that largely consists of dopamine antagonists designed to manage delusions, hallucinations and paranoia. Examples of antipsychotics are haloperidol, pimozide and aripiprazole, these are currently the only FDA approved drugs for the treatment of tics[69]. In Tourette however, the majority of the patients suffer from a variety of co-morbidities including ADHD, OCD

and anxiety related affections[43]. When treating tics in Tourette patients, these disorders should be taken into account since medicating one symptom can negatively affect any co-morbidities. The first treatment option in individuals (mostly children) suffering from ADHD often includes psychostimulants like methylphenidate, amphetamine, clonidine and guanfacine[82,83]. These psychostimulants have the opposite effects of antipsychotics, they have mechanisms of action that for example promote dopamine secretion or inhibit dopamine reuptake. Because of these opposite effects there is uncertainty regarding concurrent use of psychostimulants and antipsychotics[83,84]. Similarly treatment for OCD and disorders like depression and anxiety include the use of selective serotonin reuptake inhibitors (SSRI's)[85,86] while many antipsychotics are serotonin receptor antagonists[87].

Because of the intricate balance between pharmacologic effects, medicating Tourette patients should be performed with caution and restraint. These medications can have a variety of adverse effects on their own and combining them might not be beneficial to a large group of individuals. A study concerning long term psychostimulant using subjects taking concurrent antipsychotics found that this group has a significantly higher rate of co-morbidities and mental health issues[83]. Other than the possible danger of combining medications, these drugs have other adverse effects. Antipsychotics induce drowsiness and induce appetite resulting in weight gain. In some cases these drugs can cause extrapyramidal symptoms, mild akathisia, severe sedation, cognitive impairment and mental slowing[88]. Similarly psychostimulants in Tourette patients have been shown to cause weight loss, insomnia and obsessive compulsive behaviour[36]. Other side effects of psychostimulants include headaches, a rise in blood pressure and dyspepsia[89]. Because antipsychotics and psychostimulants have opposing effects the hypothesis has been postulated that psychostimulant treatment could induce or worsen tics in Tourette patients. Several studies investigating this phenomenon have found that psychostimulants do not induce or worsen tics significantly in Tourette patients. These studies did however find that the possibility of exacerbating tics exists in individual Tourette patients taking psychostimulants[90,91,92].

## Tourette syndrome in the future

Concerning the future of Tourette Syndrome, much is unclear. Tourette will, for the foreseeable future remain a disorder that strongly interferes with a patient's life. Many new therapies are researched and discovered while classic treatments are being improved continuously. It must however be stated that the treatment of Tourette is largely based on trial and error without understanding the underlying mechanisms. It is important that the search for therapies in this manner continues as there have been major improvements in treating Tourette patients. More knowledge about the origins of this disorder and it's comorbidities is gathered by experts and eventually large breakthroughs will take place. For this to happen new imaging technologies are needed and a larger understanding of neurobiology must be reached.

At the moment and in the foreseeable future Tourette treatments will probably remain focused on alleviating the symptoms. These therapies will improve and a large group of individuals will not experience much discomfort from the disease during their life. It remains questionable whether future treatments will be able to cure Tourette fully since the origin and mechanism of the disorder are still unknown.

For the future of Tourette, gender differences must be explored further. At the moment it is widely accepted that prevalence is higher in males than in females[9,10]. There are however theories that could explain these differences. Of course it is possible that men are more susceptible for the disorder than women, this can not be excluded or proven at the moment. It is also possible that there are just as many females with Tourette as males but that they express different or less obvious symptoms. Since the only way to diagnose Tourette is by human interpretation of tic behaviour, patients with more subtle tics could be missed. Another reason for the male : female ratio manifesting itself in this way could be that women express a different phenotype than males in most of the cases. Disorders like OCD could distort the view on tic behaviour and result in a misdiagnosis in these patients. For future generations it is important that these factors are investigated to give both males and females an optimal treatment.

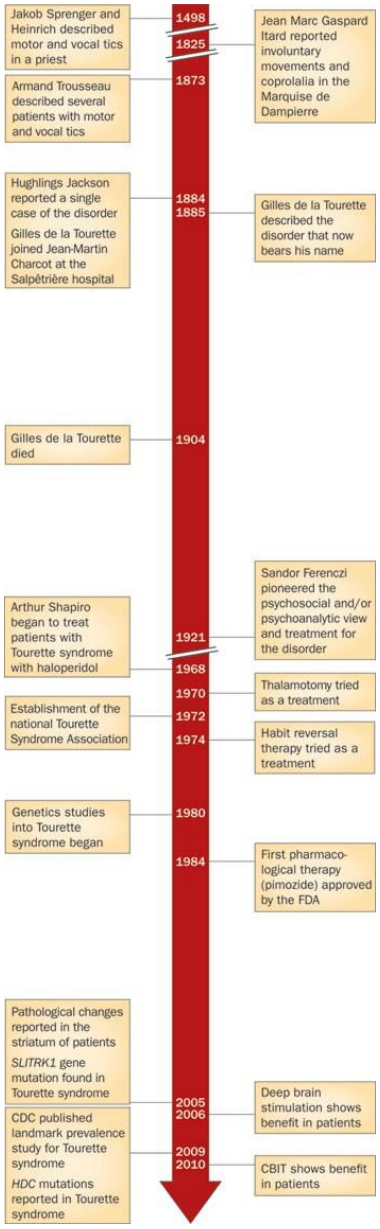


*Figure 6. Timeline of Tourette advances*[93]

## Discussion

In this paper, I tried to clarify the complexity of Tourette Syndrome and the difficulty of treating patients suffering from it. I believe that many Tourette patients in today's society are not receiving optimal treatment to improve their quality of life as much as possible. This can be solved by informing the public, physicians, therapists and everyone else involved in the life of a Tourette patient about this disorder and the different pathology phenotypes that it can induce. This way, an individual's environment can adapt and administer the right therapies for a patient.

To determine the best way to treat an individual, most often a young child, for Tourette Syndrome basic therapy sessions will remain an important first action. Experts should find out whether a child has a 'pure Tourette' phenotype or whether the patient experiences comorbidities. This is very important since every Tourette patient is unique and treating Tourette is impossible because there is no single Tourette phenotype. A decision should be made whether or not to treat a child in the first place. many children with Tourette can be helped by simply having their environment accept the disorder. This could relieve social stress and the patient can live with his or her minor symptoms.

When the tics in a patient are severe enough to discomfort them, steps should be taken to reduce these tics to a level that is acceptable. The application of CBIT as a form of habit reversal training might benefit a child greatly, the tics could become manageable and a patient can learn to understand his or her tics better. If CBIT does not deliver a satisfying improvement in tic severity other training methods might be useful. The primary treatment of minor comorbid symptoms should consist of therapy sessions and a therapist consulted by parents and patients themselves can determine if further treatments must be explored.

If a patient's tics are not alleviated to a satisfying degree invasive procedures can be considered. The first options should include therapies such as local Botox injections. If the tics consist of full body movements or do not decrease by local interventions, medicating an individual might be a solution. Medication can also be a solution in children suffering from comorbidities impairing their normal life. The problem with medication is that it can come with a lot of adverse effects. In my opinion medication should be evaded as much as possible. If medication is inevitable, patients should be monitored intensively and it might be the case that pharmacotherapy is not a viable solution in certain individuals.

In extreme cases of Tourette patients, drastic measures can be considered such as DBS. These treatments are not without risk and might decrease the quality of life of a patient instead of raising it. There are individuals that can not function in everyday life and might benefit from these interventions. Even though such extreme operations are not approved yet they are promising in some cases and can be tried as a last resort.

The goal of this paper was to give an overview of Tourette Syndrome and the complex balance of comorbidities, treatments and the course of the disease. Tourette remains a misunderstood disorder and I believe there are many aspects of the disease we do not know anything about. It is important that research on Tourette continues and that the pathology is better understood over time. The most important message of this thesis is that Tourette Syndrome is a delicate spectrum and that one patient might exhibit completely different symptoms than another patient. The key in improving Tourette therapies is therefore a personalized treatment best fitting an individual and his or her environment.

To answer the research question 'What is the current state of therapy for Tourette patients and how can Tourette treatment be optimized to best fit individuals' we must draw a disappointing conclusion. The current state of Tourette treatment is far from excellent. Many patients lack understanding of their disorder, similarly they are not completely understood by their environment resulting in the inability to receive help. Even some therapists or physicians might not fully grasp the concept of Tourette and therefore administer treatment based on the majority of individuals. This is not the way this disorder should be handled, with our current knowledge we are able to do better. Personalized medicine and insight in the broadness of the disorder could largely improve a patients quality of life. On the other

hand it is important that research continues to unfold the complex nature of Tourette. New insights and therapies could be the solution for most problems related to Tourette and might reduce this impairing disorder to a minor inconvenience.

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