Chapter 11
Tics

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
BG	Basal ganglia
CSTC	Cortico-striatal-thalamo-cortical
DA	Dopamine
DSM	Diagnostic and Statistical Manual
DTI	Diffusion-tensor imaging
GABA	γ-Aminobutyric acid
GPe	Globus pallidus externus
GPi	Globus pallidus internus
HRT	Habit reversal therapy
ICD	International classification of diseases
MPH	Methylphenidate
MSN	Medium spiny neurons
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
PANDAS	Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
PFC	Prefrontal cortex
RCT	Randomized controlled trial
REM	Rapid eye movements
SMA	Supplementary motor area

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THC Tetrahydrocannabinol
TMS Transcranial magnetic stimulation
TS Tourette syndrome

Tics: Diagnosis and Classification

Tics are sudden, patterned, repetitive movements (or sounds) resembling voluntary movements but are misplaced in context and time [1]. Single tics cannot easily be distinguished from voluntary movements phenomenologically or electrophysiologically [1]. They mainly affect the face, head, shoulders, and neck [2]. Tics can be simple involving single muscle groups (eye blinking, eye rolling, throat clearing) and complex, e.g., actions appearing intentional or compulsion-like (gestures, single words or sentences, squatting, jumping, repetitive touching) but are not goal directed [2]. Two characteristics that distinguish tics from other hyperkinetic movement disorders (except for psychogenic movement disorders and akathisia) are partial suppressibility and the fact that most TS patients, particularly affected adolescents and adults, experience tics as voluntary, intentional movements that are executed to transiently relieve an uncontrollable urge to tic [3, 4]. Tics can be subdivided into motor, phonic (vocal), cognitive, and sensory tics [5].

Phonic or vocal tics are sounds that are produced by air movement through the vocal cords, nose, or mouth such as throat clearing, barking, grunting, high-pitched sounds, or sniffing [6].

Cognitive tics or "impulsions" are repetitive thoughts, but contrary to obsessions typically observed in OCD; they are not anxiety-driven but occur as a reaction to auditory, visual, tactile, or inner stimuli that trigger the urge to tic [7, 8]. Strictly speaking, sensory tics are not tics as such but are sensations preceding a tic and are explained in more detail below (see section "Premonitory urges").

Tics are usually easy to identify and discern from other extra movements. To avoid misclassification or misdiagnosis, a general physical and neurological examination by an experienced physician is recommended by a European panel of experts [6].

Tics can resemble stereotypies. However, the latter are typically more complex and are repeated consecutively. On the other hand, stereotypies are not preceded by an inner urge to move. Some brief tics can be difficult to distinguish from myoclonus, but again myoclonus is not preceded by an urge. Also, during writing or fine finger movements, tics usually subside, whereas myoclonus is either unchanged or becomes more prominent.

Sometimes it can be challenging to distinguish between rapid tics and chorea, particularly, with outstretched arms or raised legs. Chorea, though, is unpredictable, floating, and chaotic.

In some patients with longer-lasting tonic tics, particularly affecting the neck, tics can resemble dystonia. Electromyography may help. Cocontraction of agonist and antagonist is typical for dystonia but not for tics.

Diagnostic criteria for tic disorders were defined in a very similar manner both in the tenth edition of the European *International Classification of Diseases* (ICD)-10 and in the American *Diagnostic and Statistical Manual*, fifth edition (DSM-5).

Both classification systems specify that tic disorders first occur in infancy, childhood, or adolescence and provide the following four categories: (1) TS; (2) persistent/chronic motor or vocal tic disorder, the same criteria apply as in TS, but tics are limited to either motor or vocal tics; (3) provisional tic disorder, the same criteria apply as in chronic tic disorder, but the symptoms have been present for less than 12 months; and (4) tic disorder not otherwise specified.

Tics have very rarely been associated with structural brain lesions. The number of reported patients is very small, and their clinical details are scant. In particular, in many reports it is not clear whether "symptomatic tics" were associated with preceding urges.

Tics can be induced or exacerbated by drugs (e.g., cocaine, amphetamine, antidepressants, anticonvulsants, antihistamines). Cocaine abuse is probably the most common cause of adult-onset tics. Tics are also common in autism spectrum disorders. They are sometimes part of the clinical presentation of Huntington's disease and are very typical in neuroacanthocytosis. Complex tics have been described in pantothenate kinase-associated neurodegeneration and a number of X-chromosomal disorders [9].

If a patient exhibits uncommon symptoms such as severe deterioration or adult onset, additional investigations including neuroimaging or neurophysiological techniques are recommended. Also, if the physical examination reveals dysmorphic features, or if the patient presents with learning difficulties or symptoms and signs suggestive of an autism spectrum disorder, further advise by a clinical geneticist should be sought [6].

However, as a rule, the vast majority of tic disorders belong to the TS spectrum. TS will therefore be the main focus of this chapter.

Gilles de la Tourette Syndrome

Definition

TS was first described in 1825 by the French physician Jean-Marc Itard. However, the disorder was only later named after Georges Edouard Albert Brutus Gilles de la Tourette who described nine patients suffering from what he called "maladie des tics" at the time [10]. Today, TS is defined as a neuropsychiatric disorder, acknowledging the fact that it can be successfully treated with neuroleptics and deep brain stimulation, yet has a social component to it that expresses itself in various forms such as TS patient's ability to suppress tics if socially required, or coprolalia, i.e., socially inappropriate automatic swearing.

TS is defined by the presence of multiple motor and vocal tics (not necessarily at the same time) for more than 1 year, with an onset before the age of 18. According

to the DSM-IV-TR and more recently the DSM-V, it is possible to diagnose TS in patients who experience all symptoms without reporting distress or impairment [11]. The DSM-V classifies TS as a motor disorder and groups it in the neurodevelopmental disorders category.

Defining Clinical Characteristic

Tics and Premonitory Urges

Tics in TS occur in bouts and wax and wane in frequency and intensity over hours, days, and years. The tic-repertoire typically varies across the life span in a given patient. Tics are suggestible [2] and "contagious" [12]. Patients frequently report that tics increase under stress and decrease when focused on a task, for instance, playing a musical instrument or exercising. Silva et al. (1995) identified 17 events that can cause tic exacerbation. Their main characteristic was strong emotional excitement, such as emotional trauma and social gatherings but also impending birthdays or a vacation trip [13]. Moreover, it has been shown that overall stress levels are higher in TS patients than in healthy controls [14]. However, a controlled study inducing stress experimentally in ten adolescents with TS found no increase in tic frequency under stress as compared to baseline. Tic suppression though was less effective under stress [15]. These results need to be interpreted with care due to the small sample size and the fact that only the effects of one task were measured.

Tics can be suppressed to a certain degree for a few minutes up to a few hours [2], and patients often report suppressing their tics in public or "diverting" their most obvious tic, such as facial grimacing, to less obvious movements, for instance, leg or foot movements.

For a long time it was assumed that tics are entirely automatic and uncontrollable motor phenomena. However, tics are often preceded by a premonitory sensation, an inner urge to move, which cannot be suppressed or controlled and may increase until transiently relieved by a tic [4, 16, 17]. Suppressing tics together with an increasing urge to tic can cause distress.

Premonitory sensations either can be experienced at the site where tics occur, can represent a more generalized inner tension or anxiety, or both. They are sometimes described as a pressure-like, tickling, cold, or warm sensation [18]. Overall, approximately 80 % of patients report to experience premonitory urges, depending on age and measure [19].

It is yet unclear whether urges precede, occur at the same time, or follow the onset of tics during development. Self-reports of adult TS patients suggest that first awareness of urges occurs around the age of 10, approximately 3 years after the onset of tics. However, Robertson, Leckman, and colleagues pointed out that this estimate may be due to difficulties of children at the age of 5–7 years to understand and describe the concept of urges [19, 20]. Moreover, awareness of premonitory sensations increases with age, not with tic duration, and may thus depend on cognitive development rather than time since tic onset [18].

It has been suggested that the awareness of premonitory urges improves the ability to suppress tics in some patients [20]. Banaschewski et al. (2003) investigated 254 children and adolescents aged 8–19 years. There was a significant increase in the number of children who reported premonitory sensations as well as an increasing ability to suppress tics with age. However, whereas 37 % reported premonitory sensations, 64 % were able to suppress tics. Also, only 60 % of children who gave unequivocal answers to both questions showed an overlap of premonitory sensations and the ability to suppress tics. Thus, the authors concluded that premonitory sensations are not a necessary prerequisite for tic suppression [18]. Moreover, it was shown in a sample of adults with uncomplicated TS that there was no correlation between the ability to suppress tics and the extent of premonitory urges further corroborating existing evidence that premonitory urges and the ability to suppress tics are not directly related [21].

A study investigating 100 TS patients established that premonitory urges are related to symptom severity. In patients with comorbid disorders, urges are most strongly related to OC symptoms and anxiety. Both in patients with complicated and uncomplicated TS, urges were negatively related to perceived quality of life [22].

Echo, Pali-, and Coprophenomena

In addition to tics, TS patients can have echo-, pali-, and coprophenomena. These are currently classified as complex tics, although there is some disagreement as to whether this definition is justified [23]. Paliphenomena include palipraxia, palilalia, and palilogia, i.e., the repetition of own gestures, syllables, or words [24]. Echophenomena encompass echopraxia and echolalia, i.e., the repetition of other people's gestures or sounds/words, and are relatively common in TS [12]. Imitation is considered normal in children (learning by imitation) and to a certain degree in healthy adults (e.g., contagious yawning). However, like tics, echophenomena are "exaggerated normality," misplaced in context and time [23]. Coprophenomena constitute obscene or offensive behavior such as coprolalia (involuntary swearing) and copropraxia (offensive gestures). They are extremely salient but occur only in 10–15 % of TS patients [19].

Sleep

Sleep patterns in TS patients differ from healthy controls. Adults and children with TS have lower sleep efficiency, which correlates negatively with symptom severity during the day [25, 26]. Adults have lower slow wave sleep percentage and percentage of stage 1, less number of awakenings and sleep stage changes, and increased sleep latency. Tics can occur during sleep, albeit less frequently than during the day. Also, overall movements are increased during sleep suggesting hyperarousal. This is in line with the assumption of reduced intracortical inhibition of motor pathways [25]. Rapid eye movement (REM) sleep irregularities in patients with comorbid ADHD are probably due to ADHD rather than tics [25, 26].

Comorbidities

Approximately 90 % of all TS patients suffer from comorbidities, the most common of which are ADHD (60 %) [19] and OCD (41 %) [27]. In patients with TS, OC symptoms typically occur after tic onset, around the age of 10, and remit in approximately 40 % of the patients [28]. In roughly two thirds of TS patients with comorbid ADHD, the ADHD symptoms occurred before tic onset and tend to decrease later than tics [29], while their persistence into adulthood is associated with poorer psychosocial functioning. Tic severity in childhood predicts tic severity in adulthood [27], while childhood intelligence quotient predicts the persistence of OC symptoms [27]. A smaller caudate volume in children predicts tic severity as well as OC symptoms in early adulthood [30]. The association between tics, OC symptoms, and ADHD has been assessed in a longitudinal study in a large sample ($n = 776$) that was randomly selected in the USA in 1975 [31]. The data show that tics in childhood predict an increase in OC symptoms in early adulthood. Furthermore, OC symptoms in childhood predict ADHD symptoms in adulthood, while ADHD symptoms in childhood predict OC symptoms in adulthood [31].

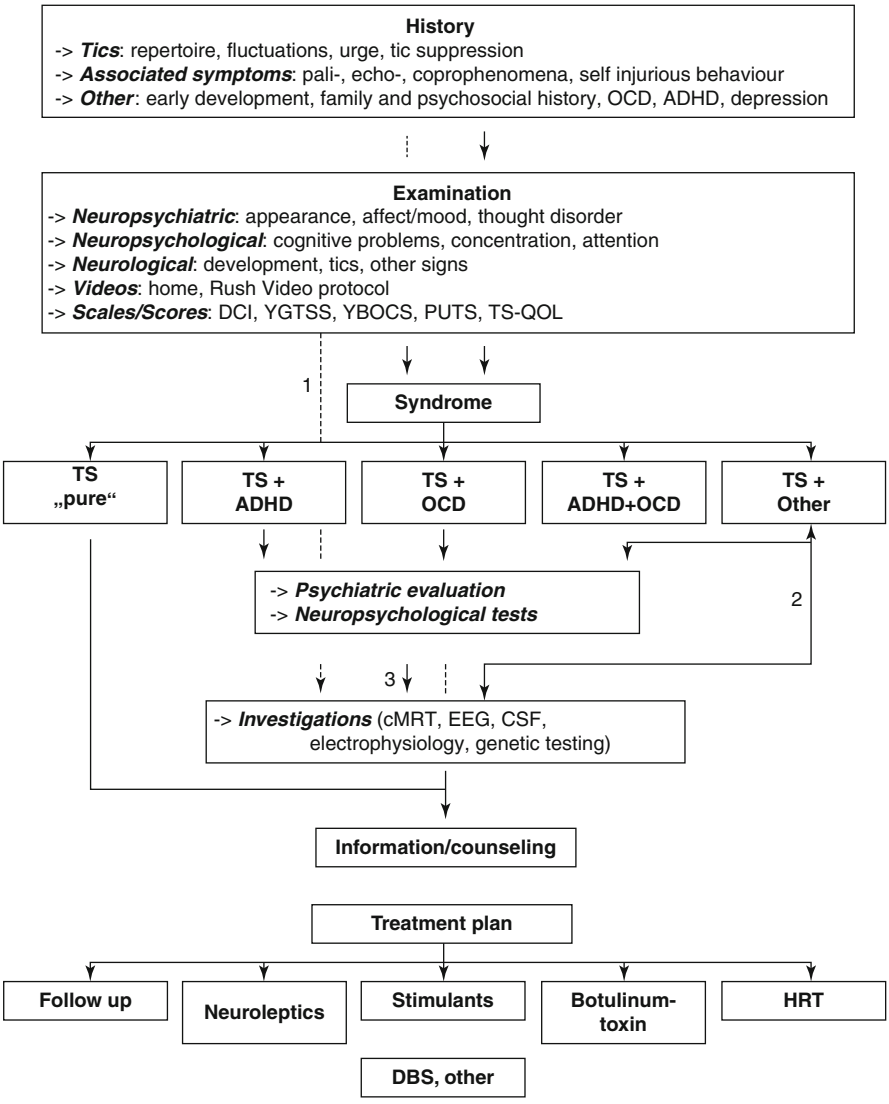
Less common are anger control problems, learning disability, mood and anxiety disorders, oppositional defiant and conduct disorders, self-injurious behavior, and autism. Males are more often affected by ADHD, conduct and oppositional defiant disorders, anger control problems, and learning disability than females, whereas females are more often affected by OCD and self-injurious behavior [32].

Fig. 11.1 Assessment of Tourette syndrome [33]. Thorough history taking including enquiring about symptoms indicative of comorbid attention deficit hyperactivity disorder (*ADHD*) and obsessive-compulsive disorder (*OCD*) is the most relevant part of the clinical assessment. It is followed by a neurological and neuropsychological examination with a particular view to signs of neurodegenerative disorders where tics might be part of the clinical presentation, e.g., Huntington's disease. Home videos can be very useful in cases where few or no tics occur in clinics. For standardized video assessment the *Rush Video protocol* has proven useful [34]. Other standardized tools include the *Diagnostic Confidence Index* (*DCI*) [35] estimating the likelihood of having Tourette syndrome, the *Yale Global Tic Severity Scale* (*YGTSS*) [36] assessing overall tic severity, the *Yale-Brown Obsessive Compulsive Scale* (*Y-BOCS*) [37] for the assessment of OCD, the *Premonitory Urge for Tics Scale* (*PUTS*) [38] addressing premonitory urges, and the TS quality of life (*GTS-QOL*) questionnaire [39]. If there are clinical indications of a comorbid disorder, further psychiatric evaluation or neuropsychological tests should be carried out. If on the grounds of the clinical examination [1, 2] or additional psychiatric/neuropsychological assessment [3], a secondary tic disorder or complex neuropsychiatric syndrome is suspected; further investigation including brain imaging, neurophysiology, and genetic testing is recommended. Following clinical assessment patients should be informed on the diagnoses and should be offered counseling. Then an individualized treatment plan is formulated. *HRT* habit reversal treatment; *DBS* deep brain stimulation (Adapted with permission from Depboylu et al. [33])

Clinical Assessment

General Approach

A diagnostic algorithm is suggested in Fig. 11.1. In children with TS, history taking should be carried out together with parents; in adult patients the partner should be present, provided patients do not wish otherwise. During clinical assessment it is of particular interest to determine which symptoms are most debilitating, when symptoms first occurred, how they developed over time, and whether there are potential



triggers and stressors. Psychosocial history should also be taken into account: how do parents or partners cope with the disorder, are there conflicts, how is the financial and housing situation, and is there a reliable social network? Complications during delivery, early development including motor milestones, and past medication and family history, particularly as regards neuropsychiatric diseases, should be documented.

Questionnaires

TS Questionnaires

For a summary of questionnaires, see Table 11.1. The number of motor and vocal tics, their severity, frequency, intensity, and complexity as well as overall impairment by these symptoms in TS and other tic disorders can be assessed with the Yale Global Tics Severity Scale (YGTSS), a clinician-rated instrument [36]. Of the existing scales, the YGTSS appears to have the best psychometric properties. It covers a broad range of symptoms. It exhibits high internal consistency, stability, and convergent as well as discriminant validity [40]. Administering the scale can take up to 20 min and requires some training on the part of the clinician. The Diagnostic Confidence Index (DCI) [35] is a questionnaire that assesses whether typical symptoms of TS are present or were present in the past. This index can be used to establish the lifetime likelihood of having TS. However, psychometric properties have yet to be investigated. The Shapiro Tourette Syndrome Severity Scale contains only five items and has high internal consistency and reliability [7]. However, it does not capture the broad phenomenology that characterizes TS. The Hopkins Motor/Vocal Tic Severity Scale is completed by clinicians and parents, assessing motor and vocal tics and associated impairment, but psychometric properties are unclear. Interrater reliability was similar for the YGTSS, Shapiro Tourette Syndrome Severity Scale, the Tourette's Syndrome-Clinical Global Impression Scale, and the Hopkins Motor/Vocal Tic Severity Scale in a sample of 20 TS patients [41].

Premonitory urges can be measured with the Premonitory Urges in Tic Disorders Scale (PUTS) [38]. The scale was originally developed for children but has recently also been evaluated in adults [42]. Psychometric properties are good, but only in individuals above the age of 10 years [17, 38]. Although the YGTSS, the DCI, and the PUTS can be recommended for clinical use, a lot more research with different age groups and larger samples is necessary to establish firm knowledge about their psychometric properties.

The YGTSS also contains one item for a quick assessment of impairment [36]. Alternatively, there is a quality of life scale specifically developed for TS patients (Gilles de la Tourette Syndrome Quality of Life Scale; GTS-QOL), encompassing four subscales for psychological problems, cognitive problems, physical/activity of daily living problems, and OC problems [39]. The scale exhibits high internal consistency and test-retest reliability as well as good content validity (judged by experts) and convergent validity (correlations with related scales) [39, 43].

Table 11.1 Summary of questionnaires

Questionnaires		
Instrument	Content	Short description
Tourette syndrome (TS)		
Diagnostic Confidence Index (DCI)	TS – lifetime likelihood	Diagnostic criteria for TS
		Psychometric properties: unknown
Yale Global Tics Severity Scale (YGTSS)	TS – number, severity, frequency, intensity, and complexity of motor and vocal tics	Clinician-rated, approx. 20 min
		Psychometric properties: good
The Shapiro Tourette Syndrome Severity Scale	TS – noticeability to others and interference of daily life	5 items
		Psychometric properties: good
		Not sufficient for covering the range of TS symptoms
The Hopkins Motor/Vocal Tic Severity Scale	TS – motor and vocal tics and associated impairment	Clinician-rated and parent-rated
		Psychometric properties: unclear
Premonitory Urges in Tic Disorders Scale (PUTS)	Tics – preceding bodily sensations/urges	Self-rated, 10 items
		Psychometric properties: good
Gilles de la Tourette Syndrome Quality of Life Scale (GTS-QOL)	TS – problems: psychological, physical, cognitive, and obsessional	Self-rated, 27 items
		Psychometric properties: good
Attention deficit hyperactivity disorder (ADHD)		
Conners 3	ADHD children – general psychopathology, inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, peer relations, family relations, ADHD inattentive, ADHD hyperactive-impulsive, ADHD combined, oppositional defiant disorder, conduct disorder	Self-report, parent-report, and teacher-report
		Long form: 99/110/115 items
		Short form: 39/43/39 items
		Screening: 10 items
		Psychometric properties: good
Conners Adults ADHD Rating Scale (CAARS)	ADHD adults – *factor-derived subscales*: inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional lability, problems with self-concept	Self-report and other-report
	DSM-IV™ ADHD subscales: DSM-IV inattentive symptoms, DSM-IV hyperactive-impulsive symptoms, DSM-IV total ADHD symptoms, ADHD index, inconsistency index	Long form: 66 items
		Short form: 26 items
		Screening: 12/18 items
		Psychometric properties: good

(continued)

Table 11.1 (continued)

Questionnaires		
Instrument	Content	Short description
The Wender Utah Rating Scale (WURS)	ADHD adults – assesses symptoms of ADHD retrospectively	Self-rating
		Long form: 61 items
		Short form: 25 items
		Psychometric properties: good
Obsessive-compulsive disorder (OCD)		
Yale-Brown Obsessive Compulsive Scale for adults (Y-BOCS) and children (CY-BOCS)	OCD adults/children – lifetime obsessive and compulsive symptoms: checking, washing and contamination, symmetry/ordering behavior, and hoarding	Clinician-rated
		10 items
		+ symptom checklist: 58–80 items
		Psychometric properties: good
Obsessive Compulsive Inventory-revised version (OCI-R)	OCD adults – doubting/checking, washing, ordering, hoarding and neutralizing	Self-rated
		18 items
		Psychometric properties: good
Obsessive-Compulsive Inventory for children (OCI-CV)	OCD children – doubting/checking, washing, ordering, hoarding, and neutralizing	21 items
		Psychometric properties: acceptable
Leyton Obsessional Inventory (LOI)	OCD adults – assesses obsessional symptoms	Self-report
		69 items
Leyton Obsessional Inventory for children (LOI-CV)	OCD children – assesses obsessional symptoms	Self-report and parent-report
		Long: 20 items
		Short: 11 items
Revised Children's Obsessive-Compulsive Inventory (CHOCI-R)	OCD children – obsessive and compulsive symptoms, degree of impairment	Self-report and parent-report
		20 items
		Psychometric properties: good

ADHD Questionnaires

ADHD should be diagnosed using standard interviews, inquiring about present and past inattention, impulsivity, and hyperactivity (starting before age 7) and integrating information from different sources. Further information should be collected about the severity, frequency, chronicity, and pervasiveness of the symptoms as well as their childhood onset and associated impairment [44]. Although not sufficient for a diagnosis, rating scales can be a useful tool to screen for ADHD symptoms. For a comprehensive review of scales assessing ADHD in children and adolescents, see [45]. For adults, the scales with the best psychometric properties and the best content validity are Conners Adult ADHD Rating Scale (CAARS) and the short

version of the Wender Utah Rating Scale (WURS) [46]. The WURS asks patients to complete questions retrospectively regarding ADHD symptoms in childhood. It is easy to use and has good psychometric properties [47].

The Conners Adult ADHD Rating Scale has several advantages over other ADHD rating scales [48]. First of all, it has a children's version, the Conners 3 (formerly Conners Rating Scale revised, CRS-R), and an adult's version, the CAARS. Secondly, it assesses impulsivity, inattention, and hyperactivity respectively in subscales and provides separate norms for different age groups and gender. Thirdly, it provides self-report scales (CAARS-S/Conners 3-SR) and observer-report scales (CAARS-O (observer)/Conners 3-P (parent)/Conners 3-T (teacher)) in a long version, a short version, and a screening for adults as well as for children. For children, Conners provides a 10-item screening instrument, the Conners 3 ADHD Index (Conners 3-AI), which can quickly identify children who should be assessed in more detail. Finally, internal consistency, interrater reliability, and validity are good.

OCD Questionnaires

The Yale-Brown Obsessive Compulsive Scale for adults (Y-BOCS) and children (CY-BOCS) encompasses ten clinician-rated items assessing obsessive and compulsive symptom severity with regard to time spent with OC symptoms, distress, interference, resistance, and degree of control over them [37]. Additionally, there is a symptom checklist of 58–80 items dealing with lifetime obsessive and compulsive symptoms concerning checking, washing and contamination, symmetry/ordering behavior, and hoarding. For adults, there is an interview version and a self-report version. Both have good psychometric properties and are equally sensitive and specific [49]. Parents are asked to complete the scale for their affected children. The Dimensional Y-BOCS (DY-BOCS) assesses symptom severity separately for each symptom cluster and adds avoidance ratings [50]. Although all three questionnaires can be recommended for clinical use, they are time consuming. Shorter alternatives are the 18-item Obsessive-Compulsive Inventory-revised version (OCI-R) [51] for adults and the 21-item OCI-CV [52] for children. The OCI-R/OCI-CV assesses six symptom domains including doubting/checking, washing, ordering, hoarding, and neutralizing. Psychometric properties are good for the OCI-R [51], but only acceptable for the OCI-CV [53].

In clinical samples, the Leyton Obsessional Inventory for both adults (LOI) and children is commonly used (LOI-CV) [54, 55]. The LOI-CV provides a self-report and a parent-report version. Sensitivity is higher in the parent-report form [56]. Self-report and parent-report versions of the revised Children's Obsessive-Compulsive Inventory (CHOCI-R) have good internal consistency, criterion validity, and convergent validity and are strongly related to each other [57]. With 14 symptom items and 6 severity items, the CHOCI is a relatively quick, but not exhaustive, measure. It is better at discriminating at the mild–moderate end of OCD in children, while the CY-BOCS discriminates better at the severe end of the disorder [57].

Neuropsychological Assessment

Motor behavior, cognitive functions, and inhibitory control are essentially normal in TS [32]. Tasks testing for manual dexterity (Purdue pegboard test) and visuomotor integration (Beery visual-motor integration test) have shown abnormalities in TS [58]. Children with uncomplicated TS exhibit enhanced cognitive control in tasks of response inhibition, such as oculomotor switching tasks, probably because tic suppression improves inhibitory control over time [59]. However, coexisting ADHD has a negative impact on cognitive performance [60]. The neuropsychological profile of coexisting TS and OCD has not been well established. However, executive function deficits have been documented in response inhibition [61] and set shifting paradigms [62]. Clinical neuropsychological assessment should be tailored to clinical needs.

Prevalence and Course

TS is 3:1 (USA) to 4.3:1 (UK) times more likely to occur in males than in females [63, 64]. It is a common disorder with a prevalence of approximately 0.3–1 % depending on the population investigated and the measures used [63–65]. Estimations of prevalence rates vary widely, due to changing definitions of TS, waxing and waning of tics, the ability to suppress tics, the decrease of tic severity over time in most affected individuals, and possibly the masking effects of comorbidities [66]. The 2007 US National Survey of Children's Health has estimated a lifetime prevalence of 0.3 % by parent report [64]. Estimates based on epidemiological studies in the UK suggest a prevalence of tic disorders in the range of 3.4–24.4 % and of TS between 0.4 and 3.8 % in children and adolescents aged 5–18 [63]. The overall international lifetime prevalence of TS is estimated to be approximately 1 % [19, 63]. TS seems to occur less frequently in Hispanics, African-Americans, and sub-Saharan black Africans [63]. Data concerning the administrative 12-month prevalence in a sample of 2.2 million individuals in Germany found a prevalence of 0.8 % for all tic disorders, indicating that TS might generally be underdiagnosed and undertreated [65]. Because most parents do not correctly classify tics as a neurological symptom, the average time until TS is diagnosed (if at all) is at least 5 years and is often followed by great relief on part of the patient [67].

The first tics typically occur around the age of 5–7 years, with vocal tics developing several months to years later [19]. Prevalence rates are highest around the age of 10 and then decrease markedly after the age of 12 [19, 65]. This probably reflects the finding that most patients experience their most severe symptoms at age 8–12 and then seek medical advice [68]. Clinical and epidemiological studies indicate that 59–85 % of patients with tic disorders are tic-free or only have mild tics upon entering adulthood [69, 70]. In the remaining 20 %, the symptoms continue or become even more pronounced after the age of 18 and often have a debilitating effect on work and social life [70]. Predictors of a worse long-term outcome include higher tic severity in childhood, smaller caudate volume, poorer fine motor skills, and untreated comorbidities [69].

Etiology

Genetic Factors

A number of findings point towards a prominent role of genetic factors, but the precise background is complex, probably polygenetic and largely unclear [71]. Family studies showed that TS and tics are 10–100 times more likely to develop in individuals who have a first-degree relative with TS [72]. TS patients are more likely than healthy controls to have first-degree family members with TS, chronic tics, and early-onset OCD, irrespective of whether patients have OC symptoms or not [72]. Interestingly, OCD is more likely to occur in female relatives, while TS is more likely to occur in male relatives. Moreover, OCD patients are more likely than healthy controls to have a family history of tics indicating that some forms of OCD and TS may share genetic influences. However, the genetic architecture (number, frequency, and distribution of genetic risk factors) of the two disorders has not been decoded, probably because there are many different genetic variations associated with an elevated risk for developing TS and OCD [73]. Recent data suggest a heritability point estimate of 0.58 for TS and 0.37 for OCD. Rare alleles (frequency <5 %) explained 21 % of the variance of TS heritability but 0 % in OCD heritability. The genetic correlation between TS and OCD was 41, confirming that there is some genetic overlap between the two disorders but that they might have distinct genetic architectures [74]. Although the DA neurotransmitter system appears to play a pivotal role in TS, no consistent association has been found between TS and DA candidate genes [75].

ADHD is also more common in family members of TS patients but is mostly accompanied by tics; hence, they may share some etiological basis but are not likely to be two phenotypical variants of the same genotype [73]. Large European and American genome studies are currently under way to identify genetic polymorphisms associated with TS (see TIC Genetics: https://tic-genetics.org).

Environmental Factors

By analogy to Sydenham's chorea, Swedo et al. suggested that tics and OCD may be sequelae of a preceding streptococcal infection [76, 77]. The acronym PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection) was suggested for a TS-like syndrome with sudden onset following streptococcal infections and a monophasic rather than undulating course. However, a causal relationship between preceding streptococcal infections and clinical symptoms has not been proven yet. In addition, the fact that some children diagnosed with PANDAS also have chorea on clinical examination raises the question of whether at least some of these children suffer from Sydenham's chorea rather than PANDAS. The role of infections and inflammatory processes in general as etiological factors in TS is currently unclear. A collaborative research project, the "European

Multicentre Tics in Children Studies (EMTICS)," funded by the European Union (7th framework programme; HEALTH.2011.2.2.1–3), addressing these issues, is currently under way.

Severe nausea of the mother in the first trimester, severe maternal psychological stress during pregnancy, and maternal consumption of more than two cups of coffee per day or more than ten cigarettes per day during pregnancy have been suggested as possible epigenetic risk factors [78]. Birth-related risk factors encompass an identical twin with lower birth weight, low birth weight with ischemic parenchymal brain lesions or enlargement of the ventricles, transient perinatal hypoxia or ischemia, and low Apgar scores shortly after birth [78, 79].

The fact that the prevalence in men is higher than in women led to the assumption that androgenic hormones may play a role during certain stages of development. Moreover, in some TS patients symptoms may be caused or exacerbated by a heightened sensitivity of the hypothalamic-pituitary-adrenal axis and thereby the noradrenergic sympathetic systems [78]. However, with the exception of birth weight and maternal smoking, the association between the factors listed above and the development of TS is weak and inconsistent [79]. Motor tics, vocal tics, depression, and anxiety in children and adolescents with TS are correlated with the number of minor negative life events (e.g., relations with family/peers, school achievements), whereas the severity of compulsions, aggression, and ADHD symptoms is correlated with the subjective evaluation of major negative life events (e.g., divorce of parents) [80].

Pathophysiology

Abnormalities in the Basal Ganglia

TS has been repeatedly associated with structural and functional changes in the BG, the thalamus, and the frontal cortex, which are implicated in the formation of habits. Habits, like tics, are stimulus-driven actions that are not outcome dependent and do not require specific attention. They are also repetitive and change over time; hence, some authors have drawn parallels between these two motor phenomena and their neural substrates with a predominant focus on the BG [81, 82]. The BG consist of several nuclei that play an important role in action selection, implementation of learned motor and cognitive sequences, and performance monitoring in goal-directed behavior. The striatum (caudate and putamen) receives the majority of its input from the cortex and the intralaminar nuclei of the thalamus and projects back to the cortex in a feedback circle that has been termed the cortico-striatal-thalamo-cortical (CSTC) loop [83].

The CSTC loops are at least partially segregated into sensorimotor, associative, and limbic loops [84]. Dysfunction of the sensorimotor loop has been associated with the development of tics, while more complex behavioral disorders might be related to dysfunctions in the associative and limbic loops [85, 86]. Neurochemically, the striatum can be divided into two parts. The matrix consists of matrisomes and

receives its input from sensorimotor areas. The striosomes receive their input from the orbitofrontal cortex (OFC), the cingulum, and the insula and are therefore part of the limbic-associative loop [87]. The neuronal population in both areas can be subdivided into 95 % medium spiny neurons (MSN), which mainly project to the globus pallidus internus (Gpi) both directly and indirectly via the globus pallidus externus (GPe) and the subthalamic nucleus, 3 % GABAergic (GABA, γ-aminobutyric acid) and 2 % cholinergic tonically firing inhibitory interneurons [87]. These inhibitory interneurons partly coordinate the activity of the MSNs throughout the striatum and thereby its output. The BG function as a break on the motor system. If inhibitory neurons, which project from the BG to the motor parts of the thalamus, increase their firing rates, motor activity will be more focused. If, on the other hand, these inhibitory neurons decrease their firing rate, more widespread motor output will be facilitated [88].

Neuropathological studies of TS have found a decreased number, as well as an abnormal distribution, of cholinergic and GABAergic inhibitory interneurons in the sensorimotor and associative areas of the striatum as compared to healthy controls [89, 90]. There seems to be an imbalance of parvalbumin-positive GABAergic interneurons with a decrease in number and density of neurons in the GPe and an increase in the GPi [89], which points to a disrupted inhibitory-excitatory balance between sensorimotor, associative, and limbic loops [90]. These alterations may foster the development of context-independent extra movements including tics. The imbalance in the BG may be caused by genetically determined aberrant neuronal migration of interneurons from the precursor of the GP to the precursor of the striatum, the cortex, and the hippocampus during embryogenesis [89].

These findings have been further corroborated by a multitude of studies employing a wide variety of research techniques. Single cell research shows that activity patterns of the MSNs and cholinergic interneurons in the putamen and GPi are correlated with tics and stimulation of the putamen can cause tic-like stereotypies in animals as well as humans (for review, please see [82]). Imaging techniques showed an abnormally high connectivity within the CSTC loops in TS patients. Changes in connectivity in the sensorimotor and associative loops were correlated with the occurrence of complex tics, while changes in the limbic and associative loops were correlated with OC symptoms [91]. Comparing tics to self-paced movements revealed increased activations in the somatosensory and premotor cortex, putamen, amygdala and hippocampus, correlating positively with tic severity and decreased activations in the caudate nucleus and anterior cingulate cortex correlating negatively with tic severity [92].

Structural and Functional Changes in Other Brain Areas

Differences in structure and function between healthy individuals and TS patients are subject to change during development [93, 94]. Resting state studies have revealed brain connectivity patterns in TS reminiscent of earlier stages of development, i.e., overall activity in adjacent areas was more strongly correlated, whereas

activity between distant areas showed lower correlations resembling correlational patterns previously found in younger healthy children, as well as adolescents with autism and ADHD [95]. Volumetric MRI showed a reduction in caudate size in children and adults with TS, whereas volumes of the amygdala, hippocampus, and thalamus were increased in children [96]. In adults, amygdala and hippocampus volumes were decreased and inversely correlated with tic severity, OC symptoms, and ADHD symptoms [93]. Diffusivity weights in children and adults with TS were altered in the BG, thalamus, nucleus accumbens, and amygdala [97, 98]. However, a study with male adolescents without comorbidities, who had never been treated pharmacologically, showed no differences in brain volume as compared to healthy controls [99]. Thus, it is largely unclear whether and to what extent differences between TS patients and healthy controls are cause or consequence of TS, OCD, and ADHD; represent adaptive changes to these disorders; or are secondary to medication.

The areas most reliably found to be thinner in cortical thickness studies in TS than in healthy controls are motor and sensory cortices in children and adolescents. Moreover, in adolescents with TS thickness was inversely correlated with worst-ever tic severity [100]. Other areas showing cortical thinning include the right dorsolateral prefrontal cortex (PFC), entorhinal cortex, OFC, parietal cortex, and cingulate cortex. Thinning of these areas may reduce inhibitory control and cause aberrant sensorimotor gating, as well as an elevated vulnerability to coexisting OCD or depression [81, 82].

Diffusion-tensor imaging (DTI) corroborates existing evidence of abnormalities in the sensorimotor cortices, showing white matter changes in motor and somatosensory circuits and fronto-striatal areas [101, 102] White matter changes have also been found in interhemispheric and transcallosal connections and were associated with interhemispheric disinhibition [103], as well as tic severity [104]. Reduced inhibition at rest has also been demonstrated by transcranial magnetic stimulation (TMS) studies [105, 106] but inhibition was normalized during movement preparation possibly because activation in subcortical regions is biased by prefrontal structures during goal-directed behavior [107].

Although TS is commonly associated with disinhibition, several studies have shown that tic severity was associated with enhanced cognitive control as well as structural changes in the PFC [59, 108]. The PFC might serve to bias response competition in motor areas rather than exert inhibitory control over other brain areas and may be hyperactive in TS patients. This hyperactivity may be compensated for in adolescence by structural and functional changes in the long-range neural pathways that link the PFC to motor areas [109]. A recent DTI study in 19 unmedicated, uncomplicated male, adult TS patients confirmed this assumption, indicating that tics might be caused by changes in PFC, thalamus, and putamen. Changes in the cingulate gyrus, however, appear to be the result of compensatory changes [110]. Moreover, volumetric changes in the PFC do not appear to be related to the ability to suppress tics [111].

Structural and Functional Brain Changes Associated with Urges

One important feature distinguishing tics from habits is the experience of premonitory urges. These are difficult to investigate though because they are subjective experiences. Some researchers suggest that premonitory urges may develop on the basis of sensorimotor and primary motor cortical inputs converging on the MSNs in the striatum [78]. Studies investigating brain activity associated with premonitory urges have yielded mixed results. Tic suppression causes activation changes in a number of brain regions including cortical areas (PFC, primary sensorimotor, temporal, parietal, and cingulate) and subcortical areas (caudate nucleus, putamen, and thalamus) [112]. Activations in the somatosensory cortices, putamen, amygdala, and hippocampus were found in another study prior to tic onset, probably reflecting the intense sensory and emotional experience of premonitory urges [92]. Moreover, the extent of experienced premonitory urges correlates positively with thickness of the primary somatosensory cortex [113]. Overall, the most consistent area associated with sensory urges so far has been the supplementary motor area (SMA) [82]. Accordingly, repetitive TMS applied over the SMA but not the primary motor or premotor cortex led to tic reduction in a pilot study [114]. Maia and Frank (2011) suggested that motor tics might initially occur coincidentally together with certain (sensorimotor) states because the likelihood of an excitatory signal relative to an inhibitory signal in the BG is overall higher in TS. Every time a movement was coupled with a certain state, a set of motor plans would also be activated in the SMA and would, via Hebbian learning mechanisms, become linked to the state over time. After a few pairings of state, SMA motor plan and BG gated action, the state would automatically cause the activation of a motor plan in the SMA, thereby producing an urge to move [115].

In conclusion, TS brains differ from healthy brains in many cortical and subcortical regions, including areas associated with motor, behavioral, emotional, and executive control, as well as memory. Well-designed, large-sample longitudinal studies, controlling for comorbidities, will be necessary to disentangle which structural and functional changes are at the heart of the disorder and which are a consequence of having lived with TS for some time.

Dopamine

Among the neurotransmitter systems that are likely implicated in TS (dopamine (DA), serotonin, noradrenaline, glutamate, GABA, acetylcholine, and opioids), DA seems to be the key player. Interactions between the systems, especially DA and serotonin, may be crucial for the development of TS but have not yet received enough attention. Results from different lines of research suggest DA imbalance/hyperactivity in TS. For instance, DA is highly active in PFC and striatum; both areas were most commonly found to be structurally and functionally altered in

TS. Direct evidence for the role of DA comes from successful pharmacological treatment of TS. While D2 DA receptor blockers (e.g., haloperidol) and DA reuptake inhibitors (e.g., tetrabenazine) improve tics, L-dopa and central nervous system stimulants such as cocaine can lead to tic exacerbation.

Precise delineation of abnormalities of dopaminergic neurotransmission in TS is difficult. First of all, DA levels in humans can only be measured indirectly. Secondly, any difference in the DA system in TS could be either the cause or the consequence of the disorder; cross-sectional data do not provide any information about causal effects. Thirdly, DA phasic and tonic levels as well as receptor density are regulated by complex feedback mechanisms. Therefore, most findings could be caused by a number of different factors. Phasic DA is released as the result of action potentials, i.e., spike dependent. Tonic DA levels represent relatively stable extracellular DA levels and depend on the diffusion rate and on DA transporters, pumping DA from the synaptic cleft back into the presynaptic neuron after an action potential occurred or releasing DA from neurons if required. Tonic DA levels stimulate autoreceptors of the presynaptic neuron, thereby regulating DA reuptake and amounts of phasic DA release. The density of D2 receptors is also regulated based on available extracellular DA concentration. Any of these factors could be altered and compensated for in TS [116]. A clear picture of whether TS symptoms are due to DA hyperinnervation, supersensitive DA receptors, presynaptic DA abnormalities, or DA tonic-phasic dysfunction, or a combination of these factors, is only starting to emerge [75, 81].

The DA hyperinnervation hypothesis postulates excessive innervation by DA terminals particularly in the striatum of TS patients. Increased DA transporter binding in the striatum in vivo and in postmortem tissue supports the notion of hyperinnervation by DA terminals. Contradictory null results in studies investigating vesicular monoamine binding, and mixed results from SPECT studies, however, suggest that the theory is not straightforward [75].

Regarding the supersensitivity of DA receptors, postmortem studies have found increased numbers of D2 receptors in the PFC of TS patients [117]. PET and SPECT studies found heightened D2 density in the caudate and left ventral striatum [118, 119], while a study investigating medication-naive TS patients found no difference [120]. Even decreased D2 binding has been reported for a number of extrastriatal regions [121].

Neuroimaging studies in humans have found increased DA transporter binding in the neostriatum and increased DA activity in the ventral striatum, increased numbers of striatal and cortical DA receptors, different binding properties in the BG, and a release of DA in TS patients after receiving a stimulant exceeding healthy controls by at least 90 % [118, 122, 123].

The most popular model is based on the tonic-phasic release of DA. Decreased tonic levels of DA in TS may lead to an increase in phasic DA release. It should also be pointed out that the brain is a homeostatic system and may adapt to dopaminergic medication over time [116]. Apart from possible side effects, this is another factor to consider and to communicate to patients when initiating treatment with antipsychotics.

To summarize, although DA appears to play an important role in the pathophysiology of TS, there is still a lot to be learned about which mechanisms are disrupted and how they interact with other neurotransmitter systems. Further insight may be gained by investigating more homogeneous samples in terms of age, TS with and without comorbidities, and medication intake.

Treatment

General Measures

Treatment should be tailored to the needs of an individual patient following thorough clinical assessment (see Fig. 11.1). Explaining the neurological background, possible comorbidities, the waxing and waning nature and the natural course of tics and TS, and its association with stress to patients and their families is the mainstay of management. Children with tics are often told to stop their tics and "behave." Therefore, communicating that tics are automatic and represent neurobiological and not psychological phenomena helps to decrease tension in families or at school. Similarly, counseling of teachers is important. A long-term relationship with a TS expert is helpful to support patients and families through the years.

TS cannot be cured. However, tic frequency and severity can be treated to a certain degree, and comorbid disorders such as OCD, ADHD, and depression can and should be treated to facilitate psychosocial functioning and support development in patients [6]. Until 2011, the only country providing explicit guidelines for the diagnosis and treatment of TS was Germany. On the basis of these, experts of the European Society for the Study of Tourette Syndrome (ESSTS) then developed the first European guidelines for the diagnosis and treatment of TS [6, 124–126]. TS can be treated with antidopaminergic medication, other drugs, THC [127], or deep brain stimulation [126]. Habit reversal therapy (HRT) has also been suggested as an option [128].

Two things should be taken into consideration before deciding on a treatment strategy. Firstly, subjective impairment does not correspond with tic severity and should be assessed independently. Secondly, for many children and adolescents, TS does not interfere with daily life. Therefore, not every tic needs to be treated.

Treatment is recommended predominantly in the following circumstances [6]. Tics are so severe that they cause pain or injuries. Pain can arise from repetitive brisk neck or limb tics leading to musculoskeletal pain. In severe cases, tics can damage joints or result in compressive myelopathy. Pain may also result directly from striking or being struck by body parts or self-injurious behavior. Some patients experience relief from tics by self-inflicted pain. Few patients report that they experience pain during tic suppression. Tics can also worsen pain such as headaches.

Tics can raise social problems such as bullying, cause stigmatization, withdrawal, depression, and anxiety, which may not be overcome by psychoeducation and counseling of patients, families, and peers alone. Salient motor and vocal tics,

especially coprolalia, can cause social friction; hence, children with TS experience more social and educational problems than healthy controls. Comorbidities can additionally aggravate these problems [129].

Pharmacological Treatment of TS

The most commonly used drugs in TS are antipsychotics, also known as neuroleptics [130]. Neuroleptics unfold their effect by blocking D2 DA receptors. Surprisingly, there are few well-conducted, double-blind, randomized controlled trials (RTC) investigating the efficacy and safety of pharmacological treatment in TS. There are two Cochrane reviews on pharmacological treatment in TS, one on the effects of cannabinoids and one on the pharmacological treatment of children with ADHD and comorbid tics. Cochrane reviews are systematic reviews that only select studies with the highest standards (randomized, placebo-controlled, double-blind). It is difficult to make recommendations based solely on the Cochrane reviews. Therefore, the authors of the European clinical guidelines for TS and other tic disorders conducted a full review of all pharmacological studies from 1979 to 2010, regardless of their quality. Their results will be summarized in the following sections (for a full review and original publications, please see [124].

Typical Antipsychotics

Haloperidol and pimozide are D2 DA receptor antagonists.
Efficacy: Pimozide and haloperidol are the most thoroughly studied antipsychotics for tic treatment and show the most consistent effects of all drugs tested. Most studies have found that both haloperidol and pimozide significantly reduce tic severity. However, haloperidol seems to consistently lead to more side effects than pimozide.

According to the Cochrane reviews, haloperidol reduces tics significantly compared to placebo. Pimozide and risperidone were less effective than haloperidol but more effective than a placebo and had fewer side effects than haloperidol [131]. A more recent meta-analysis of five high-quality RCTs testing antipsychotics (risperidone, pimozide, haloperidol, and ziprazidone) and alpha-2 agonists (adrenergic stimulants) showed that antipsychotics reduced tic severity significantly as compared to a placebo group, irrespective of the type of antipsychotic [132]. Overall, pimozide causes fewer side effects than haloperidol, especially long term. Whereas pimozide is sometimes used and recommended by TS experts, haloperidol is only very rarely used in TS specialty clinics, predominantly because of its untoward side effects.

Side effects (of D2 blockers): drowsiness, sedation, headaches, acute dystonic reaction, akathisia, parkinsonism, anxiety, hyperprolactinemia, gynecomastia, galactorrhea, irregular menses, sexual dysfunction, and significant weight gain. A combination of pimozide with macrolides and sertraline can lead to fatal QTc prolongation.

Therefore, regular ECG is recommended. Additionally, a few case reports have drawn attention to the risk of inducing tardive dyskinesia. However, this is a contentious issue. A recent systematic review found no evidence for tardive phenomena in TS [133].

Recommended dose: Dosages used in studies range from 2 to 20 mg/day for haloperidol and from 2 to 20 mg/day for pimozide. For clinical use, however, recommended doses that are typically prescribed in TS start at 0.5 mg/day. Recommended average doses for adults taking haloperidol range between 1 and 10 mg/day, with a recommended maximum between 10 and 15 mg/day. For pimozide, the recommended average dose is up to 2–8 mg/day, with a recommended maximum of 8–12 mg/day [33, 134] (for details see Table 11.2).

Fluphenazine is a D2 DA receptor antagonist, mainly used in the USA.

Efficacy: It has been shown to be effective short term and long term. In addition, it appears to cause fewer side effects than haloperidol. However, study samples were too small to draw general conclusions from these findings [124].

Recommended dose: Initial doses should range from 0.5 to 1 mg/day; treatment doses should eventually range from 1.5 to 10 mg/day [33] (see Table 11.2).

Table 11.2 Recommended doses of medications [134]

Medication					
Drug	Initial dose (mg)	Average recommended dose for adults	Recommended maximum dose (mg)	Maximum approved dose (mg)	Intake
Typical antipsychotics					
Haloperidol	0.5	1–10	10–20	100	2–3×/day
Pimozide	0.5–1	2–8	8–12	16	1×/day in the evening
Fluphenazine	0.5–1	1.5–10			
Benzamides					
Tiapride	50–100	150–600	600–800	1200	2–3×/day
Sulpiride	50–100		800–1200	1600	2×/day
Atypical antipsychotics					
Risperidone	0.5–1	1–8	4–8	16	2×/day
Ziprazidone	5–10	10–80			
Aripiprazole	2.5		10–30	30	1×/day
Noradrenergic agents					
Clonidine	0.025–0.05	0.1–0.15			
Guanfacine	0.5	0.5–1	1–4		1×/day at bedtime
Tetrabenazine	12.5		75	200	3×/day
Tetrahydrocannabinol	2.5		20–30		2–3×/day

Adapted with permission from Ludolph et al. [134]

Benzamides

Tiapride is a D2 DA receptor antagonist with very low antipsychotic action. Tiapride is also assumed to bind to serotonergic 5HT3 and 5HT4 receptors.

Efficacy: The positive effects of tiapride on tic severity have been investigated in at least eight studies. All suggested that the drug reduces tics significantly. It has to be taken into account though that most of the studies were not placebo-controlled, only one was double-blind, and the sample sizes were small [124].

Side effects: limited; drowsiness, moderate transient hyperprolactinemia, and weight gain. Tiapride did not affect cognitive performance, neurosecretory, hypothalamic-hypophyseal regulation of the sex hormones, thyroid-stimulating hormone, growth hormone, or thyroid hormone [124].

Recommended dose: For adults, the recommended target dose of tiapride is 150–600 mg/day, starting from 50 to 100 mg/day with a recommended maximum of 600–800 mg/day. For children, doses up to 300 mg/day are typically used [33, 134] (see Table 11.2).

Tiapride is a useful and generally well-tolerated treatment for tics; however, more placebo-controlled, double-blind studies in larger samples preferably with longer follow-up are needed to judge its effects more reliably.

Sulpiride is a D2 DA antagonist. It is a weak antipsychotic and, in low dosages (50–200 mg/day), weak antidepressant, stimulating, and anxiolytic drug.

Efficacy: Sulpiride significantly reduced tics in children, adolescents, and adults [135, 136]. A double-blind, placebo-controlled crossover trial in 11 patients with TS and comorbid OCD showed that sulpiride reduces tics but not OC symptoms and that fluvoxamine alone or in combination with sulpiride alleviates OC symptoms but not tics. However, although the study was well designed, only 11 patients were included limiting its power [137].

Side effects: sedation/drowsiness; often increased appetite leading to weight gain, galactorrhea/amenorrhea, restlessness, sleep disturbances, and rarely depression. Adverse reactions such as hypotension, long-QT syndrome, dry mouth, sweating, nausea, allergic rash, or pruritus are less common, and tardive dyskinesia has only been reported in one case [124].

Recommended dose: Initial doses of sulpiride range from 50 to 100 mg/day; the maximum treatment dose should not exceed 800–1200 mg/day (see Table 11.2).

Overall, D2 DA antagonists appear to reduce tics in approximately 70 % of patients. However, the disadvantages of a treatment with D2 blockers, particularly at higher doses, are potentially severe side effects [124].

Atypical Antipsychotics

Risperidone is a predominant DA antagonist (D2) but also has antiserotonergic (5-HT2) effects.

Efficacy: Several studies and case reports in patients ranging from 6 to 62 years of age suggest that the efficacy of risperidone in TS is comparable to that of haloperidol and pimozide. However, severe side effects seem to be less common [124]. Risperidone appears to be as effective as clonidine and pimozide in reducing tics, but risperidone also reduces OC symptoms [130, 138]. Risperidone may also help to treat aggressive behavior in TS.

Side effects: depressive symptoms, fatigue, somnolence, and extrapyramidal symptoms (possibly fewer than in pimozide). Although side effects seem to occur less frequently with risperidone, depression can occur [124].

Recommended dose: Risperidone can be administered in doses starting from 0.5 to 1 mg/day, with recommended average treatment doses between 1 and 8 mg/day [134] (see Table 11.2).

Clozapine cannot be recommended for treatment of TS. It can lead to increased tic severity and has potentially severe side effects [124].

Ziprazidone mainly acts as an antagonist to a variety of serotonin and DA receptors.

Efficacy: It has only been tested in one double-blind RCT and in an open-label study and reduced tics significantly compared to a placebo group [124].

Side effects: The most common adverse reaction at low doses (5–20 mg/day) was somnolence. None of the patients experienced weight gain, extrapyramidal symptoms, akathisia, tardive dyskinesia, or QT prolongation. Laboratory parameters were normal, except for prolactin. These are promising results, especially with regard to side effects. However, studies on higher doses and long-term intake of ziprazidone will be needed to determine its effects in more detail [124].

Recommended dose: Initial doses range from 5 to 10 mg/day; recommended target doses vary between 10 and 80 mg/day [33] (see Table 11.2).

Aripiprazole acts as a partial D2 DA receptor agonist, a partial agonist at 5-HT1A receptors, and as an antagonist at 5-HT2A receptors.

Efficacy: Aripiprazole has been described as effective in reducing tics in more than 200 cases. Four studies found aripiprazole unequivocally efficacious in reducing tics. Case reports suggest that aripiprazole might be a promising drug, even in TS patients who have not responded to previous pharmacological treatment. However, none of the studies was blinded or included a placebo group [124].

Side effects: weight gain, akathisia, sedation, and nausea.

Recommended dose: Aripiprazole is typically administered from 2.5 mg/day initially to 10–30 mg/day as clinically useful doses in adults [134] (see Table 11.2).

Noradrenergic Agents

Noradrenergic drugs include clonidine, guanfacine, and atomoxetine. They are most commonly used in children and adolescents with ADHD and comorbid tics. They are not as effective as antipsychotics in reducing tics.

Clonidine is an alpha-2 adrenergic drug and is used more often in the USA than in Europe.

Efficacy: The number of studies that have found a significant effect of clonidine about equals the number of studies that have not. However, a large multicenter, randomized, double-blind placebo-controlled study investigating 136 children with ADHD and comorbid chronic tic disorder showed that clonidine reduced ADHD symptoms and tic severity and was well tolerated with the exception of 28 % of patients who experienced moderate to severe sedation [139]. A randomized, double-blind, placebo-controlled multicenter study investigating a very large sample showed a significant reduction of tic severity in children and adolescents [140].

Side effects: sedation, dry mouth, headache, irritability, hypotension, and disturbed sleep. Blood pressure, heart rate, and symptoms suggestive of cardiovascular problems should be monitored during dose adjustments. Some practice guidelines specifically recommend follow-up electrocardiograms. Abrupt discontinuation can cause rebound hypertension, tics, and anxiety. There is some disagreement in the field as to the overall severity of side effects, especially with higher dosages [124].

Recommended dose: Clonidine should be started at approximately 0.025 mg/day and gradually increased until a dose of 0.1–0.15 mg/day is reached [33] (see Table 11.2).

Guanfacine is an α-2 adrenergic agonist.

Efficacy: It reduces tics and ADHD symptoms in children, but effects are small. However, its efficacy and usefulness in clinical practice remains somewhat unclear, as evidence is contradictory.

Side effects: somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea, which typically occur within the first 2 weeks of intake and then remit. Guanfacine can cause mania in susceptible children with a personal or family history of bipolar disorder. Furthermore, guanfacine can induce syncopes possibly because it can cause hypotension or bradycardia [124].

Recommended dose: Guanfacine is typically administered from 0.5 to 4 mg/day (see Table 11.2).

Atomoxetine is a selective noradrenaline reuptake inhibitor.

Efficacy: Atomoxetine has been shown to successfully reduce ADHD symptoms and tics in comorbid TS in children [141]. However, a number of case studies have reported new onset or recurrence of tics or an increase in tic severity in children treated with atomoxetine. One problem with atomoxetine is delay of onset of action, requiring 2–4 weeks of therapy before optimal therapeutic responses are achieved. Also, combination treatment with selective serotonin reuptake inhibitors must be approached very cautiously. For now, atomoxetine's effect on tics is unclear. Further studies are needed.

Side effects: increase of mean heart rate, nausea, decreased appetite, and decreased body weight [124].

Other Drugs

Tetrabenazine is a vesicular monoamine transporter type 2 antagonist. It depletes presynaptic DA and serotonin stores and blocks postsynaptic DA receptors.

Efficacy: A retrospective chart review of 77 TS patients showed a moderate to high reduction in TS symptoms in more than 80 % of patients [142].

Side effects: drowsiness/fatigue, nausea, depression, insomnia, akathisia/parkinsonism, and weight gain, but less than typically found in patients that are treated with antipsychotics. Side effects improved with lower doses. No study has reported tardive dystonia or other serious adverse reactions yet [124].

Recommended dose: Tetrabenazine is usually started at a dose of 12.5 mg/day up to 75 mg/day as an average treatment dose (see Table 11.2).

Clonazepam, a benzodiazepine, is a GABA-A receptor agonist.

Efficacy: Several studies have shown clonazepam to be effective and possibly more effective than clonidine in children. However, study samples were relatively small and no well-designed RCTs have been conducted yet.

Side effects: sedation, short-term memory problems, ataxia, paradoxic disinhibition, and dependency [124].

Because of sedation and the risk of dependency, clonazepam is not recommended as a tic treatment.

Baclofen is a GABA-B receptor agonist.

Efficacy: Baclofen reduced tics significantly in a large sample of children with TS. However, the results of a small double-blind RCT remain inconclusive [143]; hence, more evidence is needed in order to determine whether baclofen is a useful treatment for TS or not.

Side effects: sedation and drowsiness [124].

Baclofen is currently not recommended for treatment of tics.

Levetiracetam is a GABAergic drug and currently mainly used as an anticonvulsant.

Efficacy: Levetiracetam is most likely not effective as a treatment for TS [144].

Naloxone is an opioid receptor antagonist.

Efficacy: It ameliorated tics significantly in a small double-blind RCT of ten adult patients and single cases. However, doses have to be handled with care since lower doses seem to cause a decrease but higher doses may cause an increase in tics [145].

Naloxone is currently not recommended for the treatment of tics.

Nicotine can be administered as a chewing gum or a transdermal patch, and both can potentiate the effects of antipsychotic drugs, even in poor responders.

Efficacy: Randomized, double-blind placebo-controlled trials show that given together with antipsychotic agents over a timespan of approximately 2 weeks, nicotine further reduced tic severity and improved attention in adults and children/adolescents [146, 147].

Side effects: adverse gastrointestinal reactions, nausea, vomiting, and less frequently headache and sedation [124].

Nicotine is currently not recommended for the treatment of tics.

THC: Based on anecdotal evidence suggesting that consuming marijuana can attenuate symptoms in TS patients, several studies systematically investigated the effects of THC in TS and found that it alleviates symptoms without affecting cognitive performance [127]. A Cochrane review on the effectiveness of delta 9-THC reported that the effects on tic frequency and severity were small but significant [148].

Side effects: Dizziness, tiredness, and dry mouth.

Recommended dose: Up to 20–30 mg/day.

Botulinum Toxin

Local injections can be used to treat well-localized, simple motor, and vocal tics in adults and children from the age of 8. In addition to reducing tics, the treatment sometimes also reduces premonitory urges. It should be noted that the average time to response is approximately 6 days with an average response duration of about 3 months. There is good evidence that standardized treatment is objectively effective [149], but there is only a weak relation between such objective tic reduction and subjective improvement. The latter can often be achieved through individually tailored injection protocols [150]. Patients sometimes report that the treated tic "moved" to a different body region.

Side effects: temporary soreness, mild muscle weakness, and hypophonia (common in vocal tic treatment) [124].

Overall Recommendations for Pharmacological Treatment of TS

Among TS specialists, tiapride and aripiprazole are currently considered the most useful drugs for the treatment of both children and adults with TS followed by sulpiride and risperidone. Pimozide is an option in severely affected patients but has more side effects than the aforementioned drugs. In particular, QT prolongation has to be monitored. Tetrabenazine is an alternative that can be very helpful in some patients. The main limitation of this drug though is depression occurring in a considerable proportion of patients. Noradrenergic drugs including clonidine, guanfacine, and atomoxetine can be useful, particularly in children with comorbid ADHD, but their anti-tic potency is relatively weak. Although currently the only drug licensed for the treatment of TS, haloperidol is only very rarely prescribed in clinical practice. It is effective but has many side effects and is often not well tolerated. THC is a choice when other drugs have failed; it is sometimes very useful. The effectiveness of *ziprazidone is questionable. Fluphenazine, clozapine, clonazepam, baclofen, levetiracetam,* and *naloxone are not recommended. Also, nicotine is currently considered an experimental drug only.*

Behavioral Therapy

The predominant behavioral therapy for tics is the Comprehensive Behavioral Intervention for Tics. This approach combines HRT with function-based interventions that target daily life events, which typically increase tic severity. TS patients are taught to pay early attention to premonitory urges (awareness training) and use them to suppress tics by performing a competing motor response, a response that is physically incompatible with the targeted tic. Additional therapeutic elements consist of self-monitoring, relaxation training, contingency management, motivational procedures, and generalization training [151]. Exposure and response prevention interventions expose patients to the urge to tic while keeping the patient from performing the tic, to achieve habituation to the urge.

A recent meta-analysis of eight studies comprising 438 patients suggested that behavioral therapies have a significant effect over comparison conditions, which was comparable to the effect sizes found in pharmacological treatment studies [151]. Larger treatment effects were found in older patients, patients who received more therapy sessions, and patients with fewer ADHD symptoms [151]. Furthermore, an overview over five studies investigating HRT indicated that it might be more effective than a control treatment. However, one study showed that 10 months after treatment, there was no difference between treatment and control group, and another study even showed that 6 months post-treatment, the placebo group had experienced greater improvement (57.7 %) than the HRT group (46.2 %), yet the high dropout rate in this study does not allow any firm conclusions [128]. Although it has been repeatedly proposed that HRT constitutes an effective therapeutic approach, high-quality longitudinal data on the long-term effects of HRT are still lacking. Most studies suffer from small sample sizes, high dropout rates, raters not blinded to the conditions, inclusion in follow-up

studies only of patients who responded positively to the treatment, and comparison of the treatment group to itself at baseline. Given the natural course of tics, it is necessary to include a control group into longitudinal designs.

Deep Brain Stimulation

Deep brain stimulation (DBS) has been introduced as an alternative treatment option for patients suffering from severe treatment refractory TS about 10 years ago. Case reports and small, uncontrolled trials suggest some efficacy of DBS, particularly of the intralaminar nuclei of the thalamus and the GPi. However, optimal target location, stimulation parameters, and inclusion/exclusion criteria for surgery are still unclear. There are no RTCs including larger numbers of patients. Although persistent serious adverse effects are uncommon, surgery- and stimulation-related adverse events including sedation, anxiety, and apathy can occur. Among European TS and DBS experts, there is general agreement that, at the present time, DBS should only be used in adult, treatment-resistant, and severely affected TS patients, preferably in the context of controlled trials.

Treatment of Comorbidities

Comorbidities, most commonly ADHD and OCD, are present in the majority of TS patients and have to be taken into account when considering treatment goals, especially because comorbidities cause impairment more often than TS. Also, in many cases comorbid disorders are more responsive to treatment. It is often not necessary or recommendable to treat both tics and ADHD/OCD separately. An improvement in comorbidities can reduce stress and improve attention, thereby reducing tic severity. Coexisting TS does not necessarily change the treating algorithms for OCD and ADHD. Neither the treatment with stimulants, such as methylphenidate (MPH), nor its discontinuation appears to affect tic frequency or severity in children with TS. Only very high doses may lead to transient tic exacerbation [124].

A recent review on the most effective treatment of TS and coexisting ADHD concluded that, keeping the risk-benefit profile in mind, noradrenergic agents (clonidine) could be used as a first-line treatment. Reuptake inhibitors (atomoxetine) and stimulants (MPH) also appeared to be effective, but rigorous studies are still lacking [152]. A Cochrane review of 8 studies concluded that in comorbid TS and ADHD, MPH, clonidine, desipramine, dextroamphetamine, guanfacine, and atomoxetine reduced ADHD symptoms, while guanfacine, desipramine, MPH, clonidine, and the combination of MPH and clonidine improved tics significantly in children [153].

Patients with TS and comorbid OCD may not be as responsive to fluvoxamine as are uncomplicated OCD patients. In this case, coadministration of an antipsychotic should be considered.

Case Report

A 25-year-old patient presents to the TS specialty clinic. She reports that around the age of 8 years, her mother had first noticed increased coughing that persisted for several weeks to months without a throat infection. Since the age of 10 she had various extra movements including eye blinking, facial grimacing, raising eyebrows, eyes to the side, head and shoulder movements, and also noises including guinea pig whistling, throat clearing, and coughing. Symptoms fluctuated with good and bad periods that appeared to be season related. Movements were preceded by inner tension and an urge to move which was lessened after the movements. There was an increase of symptoms when she was tensed, stressed, or tired and a decrease during concentration. The patient also described forced touching of objects and bodies with a preference to do so three or five times because, as she said, she liked these numbers. Also, sometimes she would repeat words repeatedly (again three to five times). No echophenomena or coprophenomena were reported. As regards obsessive-compulsive symptoms, she had always had a habit to wash her hands three times in a row, but frequency of hand washing was not increased. She used to click on the glass with a teaspoon when drinking tea or coffee. No other obsessive thoughts or behaviors were reported. She never had any problems with concentration or attention. She reported good school performance. Occasionally, she is slightly irritated when asked to abstain from certain movements. There are no aggressive behaviors and no rage attacks. Past medical history is unremarkable.

The patient is currently studying economics. She is married and has a 4-year-old healthy daughter. Her father also had facial and neck tics when he was younger and still excessively blinks at times. Her mother is described as a very orderly person. She regularly spends several hours a week evening up household items in addition to keeping the house very tidy. There is no other family history of note. The patient has not tried medication yet.

On examination she is friendly, but slightly guarded and tensed with variable eye contact. She is euthymic and there is no thought disorder. She has multiple motor and phonic tics including facial grimacing, raising eyebrows, head to the side, head and shoulder movements, trunk movements, and also complex arm movements like raising the hand, putting it in front of the shoulder, throat clearing, and coughing. There are also echophenomena when facial tics were imitated by the examiner. The remainder of the neurological examination is normal.

In summary, this patient has a typical history of multiple motor and phonic tics with onset before the age of 18 and a duration of more than 1 year. Also, tics are preceded by premonitory sensations and fluctuate in a typical way so that a diagnosis of TS can be made. The patient also has palilalia, echolalia, and several "just right phenomena." There is no indication that she has comorbid OCD or ADHD, but family history is suggestive of OCD in the mother and TS in the father.

In clinics, the neurobiological basis of tics and associated phenomena is discussed and the diagnosis of TS explained. It is pointed out that currently the underlying cause of TS is unclear with genetic factors likely playing a prominent role. Given

the patient's concern that her symptoms might solely be caused by stress, it is clarified that tics are no psychological phenomena. The patient wishes medical treatment. As first-line drug tiapride is recommended with an initial dose of 50 mg twice daily to be gradually increased to 100 mg three times a day if required and tolerated. As an alternative treatment, aripiprazole is suggested. The patient was given a follow-up appointment in 3 months' time.

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