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EDITORIAL

European clinical guidelines for Tourette Syndrome and other tic disorders

Veit Roessner · Aribert Rothenberger · Hugh Rickards · Pieter J. Hoekstra

After the first description by the French neurologist Georges Gilles de la Tourette in 1885 [3], Tourette Syndrome (TS) has fascinated many clinicians and researchers over the decades. But to date there are relatively few studies on tic disorders (PubMed search 29 January 2011, $n = 1{,}283$) and TS ($n = 3{,}762$) compared to other neurodevelopmental disorders with onset in childhood such as attention/deficit-hyperactivity disorder (ADHD, $n = 18{,}572$) or obsessive–compulsive disorders (OCD, $n = 12{,}558$). Thus it is not surprising that the evidence base on etiology, assessment, and treatment is still limited, although there is a high level of clinical experience, particularly in specialized centers.

One of the many reasons for the small base of high-quality evidence in diagnosing and treating children and adolescents with TS could be seen in the fact that it has only recently become evident that TS and other tic disorders are not rare at all [10] and may negatively impact the quality of life of those affected. This underestimation, in combination with a high rate of relatively mild cases and an often favorable course, with good chance of spontaneous remission, might explain why the necessity for studying TS has been neglected.

The progress of methodologically sound research in the field of TS has been further hampered by the fact that tics show an extremely high variability over time in frequency, severity, complexity, localization and chronicity [5], which requires long-term observations in large samples. In addition it is not straightforward which specialty should deal with TS, a cause for further fragmentation. The core symptoms of TS (i.e., tics) could be seen as a neurologic hyperkinetic movement disorder. However, its neurodevelopmental character and the high rate of different comorbidities, e.g. attention-deficit/hyperactivity disorder (ADHD) or obsessive–compulsive disorders (OCD) suggest its allocation to child and adolescent psychiatry. Although this has triggered a lively interdisciplinary dialogue it might, on the other hand, be one further cause for the lack of strong and large (inter)national research projects in this field.

To overcome this unsatisfactory situation the European Society for the Study of Tourette Syndrome (ESSTS) has been established (originally in 2000 in Copenhagen by Prof. Mary Robertson and others, but re-established in 2008 in Bari after a prolonged silent period). Membership is open to European clinicians and researchers who have an interest in TS. The aims of ESSTS are:

- to enhance understanding of the causes of TS,
- to find effective treatments for TS,
- to share good practice, and
- to stimulate European collaboration in research.

These guidelines represent the collective view of expert clinicians in the area and are not intended to be rules and conditions since rules and conditions in different countries may vary, such as drug licensing or the availability of therapists.

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Therefore we as ESSTS members have decided at our annual meeting in Leiden 2008 to join the forces by developing the first version of European clinical guidelines for TS and other tic disorders. This seemed particularly relevant as ESSTS contains a lot of clinical and research expertise on TS from different disciplines across Europe, while the only three existing Cochrane Reviews on the treatment of tics in TS are all limited to pharmacological treatment [1, 8, 9] and came to the same conclusion, i.e. that the evidence for efficacy and safety of the studied drugs does not allow firm recommendations. This undesirable situation is also reflected by the fact that to the best of our knowledge in Europe there are currently only national guidelines in Germany [6, 11]. In addition, while there have been several excellent reviews on the assessment and treatment of TS, these have typically failed to use systematic criteria of study selection [2, 4, 7].

Despite existing wide variations from even tertiary center to tertiary center across Europe, we are proud to present the first version of European clinical guidelines for TS and other tic disorders. We have set up writing groups working on thorough literature review for existing evidence base, adding clinical experience and expertise including intensive and fruitful discussions within ESTSS during the last 2 years. These guidelines hopefully will help clinicians to offer the best clinical service to affected children, adolescents, and adults and inspire clinical researchers as well as politicians to no longer overlook the high burden of tic disorders.

Conflict of interest Commercial firms and governmental organisations did not play a role in, or fund, the development of these guidelines. Hugh Rickards declares that he has no conflict of interest. Veit Roessner: has received lecture fees from Eli Lilly, Janssen-Cilag, Medice, Novartis, he was member of advisory boards of Eli Lilly, Novartis; Aribert Rothenberger (last 3 years): Advisory Board and Speakers Bureau of Lilly, Shire, Medice, Novartis, Research Support from Shire, German Research Society, Schwaabe, Travel Support from Shire, Educational Grant from Shire, Consultant of UCB/Shire, Lilly; Pieter J. Hoekstra: has received lecture fees from Eli Lilly, the University of Frankfurt, Boerhaave, Congress care, and Benecke, has received research funds from ZonMw, NWO (Netherlands Science Foundation), and the European Union (7th Framework Programme); travel support through the European Union (COST action and European Science Foundation); he was member of advisory boards of Eli Lilly and Shire, and paid consultant for Desitin and has been involved in an investigator-initiated trial sponsored by Eli Lilly.

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European clinical guidelines for Tourette Syndrome and other tic disorders. Part I: assessment

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Abstract A working group of the European Society for the Study of Tourette Syndrome (ESSTS) has developed the first European assessment guidelines of Tourette Syndrome (TS). The available literature including national guidelines was thoroughly screened and extensively discussed in the expert group of ESSTS members. Detailed clinical assessment guidelines of tic disorders and their comorbidities in both children and adults are presented. Screening methods that might be helpful and necessary for specialists' differential diagnosis process are suggested in order to further analyse cognitive abilities, emotional functions and motor skills. Besides clinical interviews and physical examination, additional specific tools (questionnaires, checklists and neuropsychological tests) are recommended.

Keywords Tics · Tourette · Assessment · Guidelines

Introduction

Tics are defined as sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations usually appearing in bouts while waxing and waning in frequency, intensity and

Members of the ESSTS Guidelines Group are given in Appendix.

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kind of tic [1]. Tic disorders including Gilles de la Tourette or Tourette Syndrome (TS) typically onset in childhood mostly at the age of 5 to 6 years [2, 3]. TS encompasses the combination of chronic (more than 1 year) motor and vocal tics. TS is often underdiagnosed and many patients do not receive adequate information and care [5, 6], and thus suffer from psychosocial impairment for a long time. On average, it takes more than 5 years from first onset of symptoms to diagnosis [7]. Patients and their families are frequently unable to correctly identify the symptoms and patients sometimes get stigmatised as a consequence of their tics. Therefore, they often experience a great relief to get a diagnosis because this allows them to better cope with the situation. There is no cure for TS, therefore, treatment aims to diminish tic severity and frequency. Often it is more important to manage the commonly comorbid conditions in order to improve psychosocial functioning and development. So far, to the best of our knowledge, only in Germany explicit guidelines for the diagnosis and treatment of TS exist (German Guidelines of child and adolescent psychiatry [8] and neurology [9]). In the past years, there has been an increasing interest in research on aetiology, pathophysiology, diagnosing and treatment of TS, leading to valuable new insights on many aspects of the syndrome. Therefore, experts of the European Society for the Study of Tourette Syndrome (ESSTS) have developed the first European guideline in four parts (this issue). This part deals with the assessment of tic disorders in children, adolescents and adults.

Epidemiology of tics

Prevalence

TS affects between 0.3 [10] and 1% [11] of the population, a.o. depending on age of the study group and rigorousness of the sampling method used. Tics occur predominantly in young people (before age 18), and tend to have a waxing and waning course [12]. Importantly, a TS diagnosis is twice more likely to occur in non-Hispanic white persons than in Black persons or in Hispanics [10]. There is a male to female preponderance of between 3:1 [10] and 4.3:1 [13, 14].

Course

The mean age at onset is around 5 years although lower ages at onset are reported in up to 40% of persons. Waxing and waning is the rule. Complex tics generally appear later than simple ones and phonic tics appear later than motor tics [15], usually after 1 or 2 years, with <5% of patients developing phonic tics first [16]. For most patients, the worst ever period of tics occurs between 8–12 years of age [17, 18].

The course of tics is relatively favourable over time. Clinical as well as population-based studies indicate that up to 80% of persons who have presented with a tic disorder before age 10 experience a significant tic decrease during adolescence, and by age 18 tic intensity and frequency has decreased to such an extent that the person no longer experiences any impairment from tics, although objective ratings indicate that most persons still have mild tics [19]. Yet, a small proportion of patients (20%) does not experience a decrease in tic intensity, and in this group some individuals not only experience tic worsening in adulthood but develop the most severe and debilitating forms of tic disorders. Reports on whether certain types of tics in childhood predict tics or comorbidity in adulthood are somewhat conflicting [20–26]. Frequency and severity of tics in childhood is hardly predictive of tic severity in adulthood [22]. However, children and adolescents with tics experience worse quality of life than healthy children (but better than psychiatric controls) [27], and poorer quality of life is related to increased tic severity [28]. Poor quality of life in adults with TS is associated with persistence of OCD [29]. Comorbid OC symptoms in children with TS onset at a somewhat later age (around 10 years) than tics and, in children with tics, tend to remit in only about 40% of patients [29]. Further new onset of OCD at a later age might occur [12]. Interestingly, persistence of OC symptoms into adulthood is particularly related to high IQ, and to smaller caudate volume measures in children [23, 30].

ADHD symptoms in TS children occur in the majority of cases before tic onset, and in one third of children after tic onset [31]. ADHD symptoms tend to decrease in 20% of children during adolescence but later than tics. Interestingly, OC symptoms in childhood predict OC symptoms and more ADHD symptoms in adolescence and adulthood, and ADHD in childhood predicts more OCD in adulthood [17, 26]. Finally, persistence of ADHD into adulthood is related to poorer psychosocial functioning. In conclusion, the following picture emerges: as tics in childhood hardly predict long-term outcome, comorbid OCD and ADHD are associated with poorer psychosocial functioning.

Pathogenesis

Family studies of TS consistently show a 10- to 100-fold increase in the rates of tics and TS in first degree relatives of TS patients compared to control families, indicating a strong genetic component to be operant in the disease [31–33]. Tic severity increases with bi-lineal transmission [34]. Further, independently of whether the proband has

concurrent OCD, first degree family members of TS patients have elevated rates of early-onset OCD, especially the female relatives, suggesting that—in TS—OCD is an alternate expression of the TS phenotype [32]. With respect to ADHD transmission, the picture is slightly different; although rates in first degree relatives of TS families are significantly elevated, ADHD is mostly comorbid with tics in the relatives, pointing into the direction of shared aetiology, i.e. associated but not comorbid in the strict sense [35], and not ADHD as an alternate expression of the disease [31]. In summary, these family studies strongly indicate a genetic component to be operant in TS, with shared genetic influences between tic and OCD, but it is unclear for ADHD. A large Genome Wide Association Study within the TSA genetic consortium is underway [36] (for a review on the genetics of TS: see O'Rourke et al. [37]).

MRI studies with different techniques [38–43] and electrophysiological investigations [44] on neuronal inhibition have identified alterations in brain areas of the cortico-striato-thalamo-cortical (CSTC) circuits. Finally, PET raclopride studies using amphetamine challenge to study D2 receptor availability in striatal circuits in TS patients have revealed increased phasic dopamine release in ventral striatal areas in TS patients after amphetamine challenge [45, 46] (Table 1).

Diagnosing

Tics can either be diagnosed according to the tenth International Classification of Disease (ICD)-10 criteria or according to criteria of the Diagnostic and Statistical Manual Text Revision, fourth edition (DSM-IV-TR) [47]. These classification systems are fully compatible. According to DSM-IV-TR criteria, tic disorders are grouped under the disorders that first occur in infancy, childhood or adolescence, and encompass four categories, i.e. Tourette's disorder (307.23), chronic motor or vocal tic disorder (307.22), transient tic disorder (307.21) and tic disorder not otherwise specified (307.20) (Table 2). In ICD 10, the same categories exist and the differences are minimal. In DSM-IV-TR [4] one item has been omitted that is mentioned for nearly all mental disorders and has previously been necessary for the diagnosis of TS: "*The disturbance causes marked distress or significant impairment in social, occupational or other important areas of functioning*". This modification was made in recognition of the fact that clinicians see patients who meet all the other criteria for TS, but do not have distress or impairment.

For DSM-V (expected in 2013), only minor changes have been recommended, designed to clarify and simplify the diagnostic criteria, and reduce the use of the tic disorder not otherwise specified category. A European commentary on recent DSM-V version can be found in this Journal [48]. Specific recommendations include a.o: (1) simplification of the duration criterion for the tic disorders; any person who has tic symptoms of less than 12 month duration but more than 4 weeks duration receives the diagnosis 'provisional tic disorder'; (2) establishing new tic disorder categories for substance induced tic disorder and tic disorder due to a general medical condition; (3) including a motor tic only and vocal tic only specifier for the chronic motor or vocal tic disorder category [49].

To establish a diagnosis of TS, a person must have (1) the combination of two or more motor tics and one (or more) phonic tic, that have been present at some time during the illness although not necessarily concurrently; (2) tics occur many times daily nearly every day through a period of more than 1 year; (3) onset before 18 years of age; and (4) are not directly caused by a general medical condition or by substance use.

Table 1 Clinical features of tic disorders to be distinguished from similar phenomena of other disorders; MED medication induced

Tic phenomena	Differential diagnosis
Eye rolling	Absences
Focussing on tic control	Attention problem
Tic repetition (after post-tic urge)	Obsessive–compulsive behaviour (OCB)
"Excessive" tic	Imitation/somatisation
Tripping	MED-akathasia, juvenile Parkinson desease/OCB
Neck jerking a.o.	Dystonia, MED-dyskinesia
Convulsive grimacing	Blepharospasmus/Facialis spasm
'Slinging' tics	Chorea
'Trembling' tics	Myoklonus
Monotone tic ('rhythmic')	Stereotypy
Tics during sleep	Restless legs/Rolandi epilepsia/ parasomnias
Excesive eye squeezing in adults	Blepharospasm

Table 2 Differences of motor symptoms in ADHD and tic disorders

Tic disorders	ADHD
Fragments of normal movements	Generally increased motor activity
Circumscribed functional muscle groups	General motor hyperactivity
Suddenly occurring (independent of waiting situation)	Slowly increasing (intensified by waiting situation)
Fixed pattern of quick actions	Disorganised, tempo change
Badly modulated	Badly modulated
Uniformly repeated (often in bouts)	Temporally irregular-intermittent (changing intensity)

Motor tics are described as brief, sudden, irresistible, inapposite and non-rhythmic recurrent movements in voluntary muscles or muscle groups [50]. Most common tics occur in the face, neck or shoulder musculature and encompass a.o.: eye blinking, nose and mouth twitches and shoulder jerks.

Vocal tics are defined as sounds elicited by a flow of air through the vocal cords, mouth or nose and the most common vocal tics are: throat clearing, grunts, high-pitched sounds and sniffing. Amongst the most well-known vocal tics is coprolalia (i.e. the uttering of socially inappropriate words), which occurs only in between 14 and 20% of patients [51]. Tics can be suppressed or inhibited depending on the situation. The suppression, however, causes an uncomfortable sensation.

Three essential 'tic' features can be recognised that are closely interwoven, i.e.: (1) temporary tic suppression [16]; (2) inner tension that accompanies tic suppression; (3) the feeling of active involvement in performing a tic, especially in adults. Although patients cannot permanently suppress the tic they might experience the tic as a conscious, intentional and self-directed movement executed to relieve a premonitory urge [52]. This feeling of intentionality is rarely present in children between age 4 and 8 but increases with age, and by age 12 the majority of patients recognises a premonitory urge preceding and exacerbating a tic [15]. This subjective perception is an important distinguishing feature from other hyperkinetic movement disorders [52].

Tics usually start in the face and tend to extend caudally, with a remaining preference for head, neck, shoulders and arms. Tics tend to significantly decrease during sleep, although—in contrast with previous notions—they often do not disappear [53]. Up to 60% of TS children and adults complain about disturbed sleep [54]. Polysomnography and simultaneous video recording during sleep in TS patients has revealed both an increased number of regular movements and more tics in all sleep stages but especially during REM sleep [53, 55, 56]. Patients show decreased sleep efficiency and slow wave sleep percentage, increased sleep latency, more awakeness and awakenings and more sleep stage changes during sleep. Severity of TS is positively associated with number of awakenings and sleep stage changes and negatively with sleep efficiency. Comorbid ADHD, a condition in which increased motor activity during sleep is found as well, seems to significantly add to the sleep problems in TS [56–58].

The intensity of tics depends in most cases on environmental cues, such as exciting or stressful events, although the nature of these environmental mediators has hardly been investigated systematically yet. In apparent contrast to this, tics can exacerbate during relaxation, for example whilst watching television. Situations or activities that require focused attention from the patient often diminish tics, both in children and adults [59].

Types of tics

Tics can be classified according to: type, complexity, whether they are isolated or multiple, and according to location, number, frequency and duration [6]. They also vary in terms of intensity or 'forcefulness' [69].

Type

Tics can be motor, vocal, sensory or cognitive [60].

Motor tics

Motor tics arise in the voluntary musculature and involve discrete muscles or muscle groups. Tics can be seen as fragments of normal motor movements that appear out of context [61]. The most frequent tic is eye blinking. [16].

Phonic (or vocal) tics

Phonic (or vocal) tics can consist of any noise produced by movement of air through the nose, mouth or pharynx. Tongue clicking is, therefore, not classified as a phonic, but a motor tic. The term 'phonic' should be preferred over 'vocal', since not all sounds (f.i. sniffing) are produced by the vocal cords. Less than 5% of patients with tics have phonic tics alone without associated motor ones [62], but motor tics without phonic tics are very common.

Sensory tics

Many adult patients (up to 90%), are aware of premonitory sensations preceding the tics, with a mean age of starting to become aware of 10 years, and depending on type of tic [15]. More automatic movements such as eye blinking are less often preceded by sensory urges. These sensations are experienced as unpleasant somatosensory sensations, either within the muscles of the upcoming tic or somewhere else in the body or the head (tiredness, itch, pressure, stabbing pain, abdominal discomfort, heat or cold) and sometimes difficult to articulate. They are often relieved by execution of the tic [52, 63]. Younger children are much less aware of premonitory urges; 37% of children between 8 and 19 years are able to report on premonitory urges, whereas 64% of these children were able to suppress their tics. Thus, tic awareness does not seem to be a prerequisite for the ability to suppress tics, and awareness seems to increase with age, and be closely associated with cognitive development [64]. Premonitory urges can be bound to small

localised areas, with 'hot spots' in the shoulder girdle, hands, feet and front of the thighs. They can also be more generalised, and described as a sense of 'inner tension' [61].

Cognitive tics

These tics have been described in adolescents and adults with TS and seem to occur predominantly in this age group [65–67]. They have been first described by Shapiro et al. [16] and termed 'impulsions' to delineate them from the anxiety-driven 'obsessions' that occur in 'pure' OCD patients. Thus, cognitive tics are described as repetitive thoughts that are not anxiety-driven but occur as a response to the excessive urge to give in or act upon provocative auditory, visual, tactile or inner stimuli [67]. Although exact frequencies are not known, cognitive tics encompass: echophenomena in thought, mental play [68], aimless counting and repetitive thoughts with sexual or aggressive content that produce no fear.

Complexity

Tics can be subdivided into simple and complex [62]. Simple tics are restricted to one muscle or a single muscle group. Examples of simple motor tics are: eye blinking, nose twitching, tongue protrusion, head jerks and shoulder shrugs, etc. Examples of simple phonic tic are grunting, throat clearing, coughing, sniffling and barking, etc.

Complex motor tics often have a repetitive and/or compulsive nature. Examples are: the repetitive touching of objects or people, making elaborate sequences of movements, repetitive obscene movements (copropraxia), mimicking others (echopraxia) or wounding oneself (self-injurious behaviour). Complex phonic tics occur when sounds are elaborate or have a semantic content, including for instance words or phrases, expressing obscenities (coprolalia), repeating others (echolalia) or repeating oneself (palilalia). In general, complex motor tics are aimless or in response to an excessive premonitory urge. However, when the tic sequences are complex and elaborate it can be difficult to distinguish them from compulsions as seen in 'pure' OCD, the latter being more cognitively driven, goal-directed and aimed at reduction of anxiety [15].

Isolated or multiple

One can have one tic that always originates from the same anatomical location (isolated) or many tics at multiple locations. Migration of tics from one location to another over longer periods of time is typical in chronic tic disorders. The tics wax and wane in intensity and complexity.

Duration

Tics are generally brief. They can be categorised as clonic (less than 100 ms) or dystonic and tonic (more than 300 ms). Dystonic tics are less common and are characterised by a repetitively abnormal posture of a kind that one may see in dystonia (e.g torticollis). In tonic tics, there is a relatively long duration of the contraction (in e.g. back muscles) without exhibiting abnormal postures.

Impairment

In children and in adults, it is paramount to assess degree of impairment due to tics or comorbid conditions, although as described here above, in DSM-IV-TR [4] and in future DSM-V [49], the distress item has been omitted that was obligatory to establish a tic diagnosis in previous classifications. Impairment entails that the disorder is time consuming, causes significant distress and interferes with major domains of daily life of both children and adults, such as school, work status and (social) relationships. Impairment can be reliably measured with various instruments, including the impairment item on the Yale Global Tic Severity Scale (YGTSS), which separately rates impairment due to motor or vocal tics, on 0–4 scales [69]. Alternatively, impairment can be assessed using a Global Assessment of Functioning, both in children (C-GAS) [70] and in adults according to axis five of DSM-IV TR (2002 [47]). The scale runs from 0–90, with 0 indicating complete dependence on care by others, and 90 being healthy and excellently functioning in all areas of development, school/work and psychosocial functioning. Further, in children as well as adults the Clinical Global Impression Scale (CGI-S [71]) can be rated by the clinician. The CGI-S assesses change in global daily functioning (between 0 = much deteriorated and, via 3 = no change, to 6 = very much improved). The CGI-S has shown good face validity and is extremely easy to use, although interrater reliability is somewhat low [72].

Recently, a Quality of Life scale has been developed specifically for tic disorder patients [73, 74]. This 27 item scale is based on the health-related quality of life scale (HR-QOL) [75] with response ranges between 0 and 4, and assesses quality of life in four domains: psychological problems, cognitive problems, physical/Activity of Daily Living problems and obsessive–compulsive themes. Internal consistency as well as test–retest reliability are excellent. TS patients report elevated scores, predominantly in the domains of psychological and cognitive problems [73].

Comorbidity

In clinical series, the large majority of cases (79%) have comorbid psychopathology, with attention deficit/hyperactivity disorder (ADHD) predominantly of the inattentive or combined subtype, being the most frequent comorbid disorder in up to 60% of the cases in both children and adults [31], followed by Obsessive–Compulsive Disorders (OCD), merely in adolescents and adults, anger control problems, sleep disorder, learning disorders, mood disorders, anxiety disorders and conduct and oppositional defiant disorders (CD/ODD). Sex differences occur with respect to this comorbidity, with predominance of males over females for ADHD, CD/ODD, anger control problems and learning disorders, and a female preponderance for OCD and self-injurious behaviour. Other comorbidities include impulsive, self-injurious and aggressive behaviour, autism spectrum disorders and sleep disorders [76]. Especially in adults, comorbidity often forms the main reason to seek help.

Differential diagnosis

Tics need to be differentiated from other hyperkinetic movement disorders and from psychogenic movement disorders (Table 3). The features that distinguish tics from other movement disorders—with the exception of akathisia and psychogenic movement disorders—are (1) the ability to suppress them for a while, and (2) the patient's experience of tics as a (partly) voluntary movement to relieve an inner tension or a premonitory focal sensory sensation [77]. These features can be used to help differentiate from other movement disorders which characteristically worsen with action and are not suppressible [78] (Fig. 1).

Table 3 Clinical differences and similarities of tic disorders and obsessive–compulsive disorders

Tic	Obsessive–compulsive disorder
Differences	
Sudden, short (jerking)	Ritualized
Fragmented movements	Goal-directed behaviour
Sensorimotor urges	Thoughts/imaginations (cognitive-emotional dissonance)
Not related to anxiety	Mostly related to anxiety
Ego-syntonic	Ego-dystonic
Involuntary (clustered sequence)	Voluntary (cyclic)
Onset in primary school (one peak)	Onset after primary school (two peaks)
Waxing and waning (from seconds to months)	Little changes over time
Also during sleep	Never during sleep
Similarities	
Decrease with concentration	Decrease with concentration
Increase with emotional excitement	Increase with emotional excitement
Suppressible (short-term)	Suppressible (long-term)

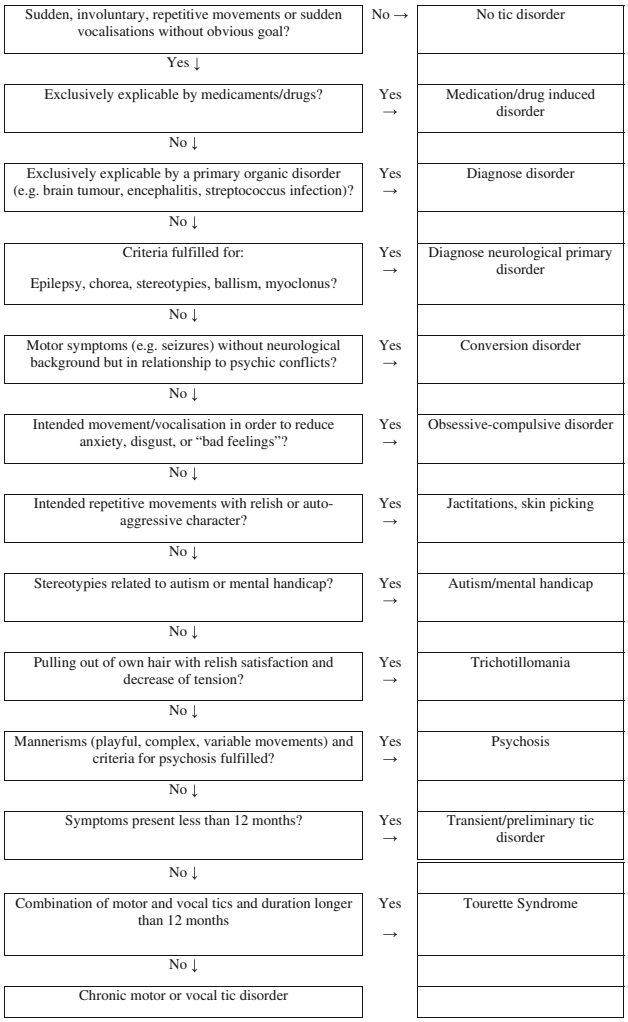

Fig. 1 Differential diagnostic decision tree for tic disorders

Work up

General evaluation

A *general evaluation* of both children and adults includes assessment of the most debilitating complaints and symptoms, assesses how the symptoms developed and inquires about potential stressors and triggers. Especially in children, a developmental history is obtained. In children and adolescents, family functioning is assessed including parental coping styles and parental conflict, social network

and financial & housing situation. In adults, partner status, current work and financial/housing situation is assessed as well. Moreover, if available hetero-anamnesis on tic and disease status is obtained from a partner, spouse or confidential person in the vicinity of the adult patient.

Parent- and patient rating scales to support the general evaluation

In children, adolescents as well as adults, it is highly advisable to supplement clinical interviewing with screens that rate general psychopathology. In children and adolescents, these are parent and/or teacher-derived, in adolescents complemented with self-reports, and in adults self-reports are taken, when necessary complemented with hetero-anamnestic assessments of a partner, parent or other person in the neighbourhood of the patient.

Self-report scales are recommended to provide general information on psychopathology. In children and adolescents, the parent-derived Child Behaviour checklist (CBCL) or—in adolescents and adults—the Young Adolescent Self-report or Youth Self-report which is fully in line, is highly recommended [79–81]. The same holds true for the SDQ (Strengths and Difficulties Questionnaire [82]; see also internet at www.sdqinfo.com). These scales are well validated across the different age groups, providing the clinician with the opportunity to follow children across the lifespan essentially using the same scale.

A detailed medical history is conducted (including medication and drug consumption in pregnancy by the mother, birth history, early development and past medication use by the patient etc.), and a complete psychosocial and family history to detect psychiatric and/or neurological conditions in relatives.

Interviews to assess disorders of infancy, childhood and adolescence including tics are abundant in child psychiatric settings. Various interviews are (1) compatible with international diagnostic systems (DSM-IV and/or ICD-10), and (2) explore the whole range of childhood derived disorders [83]. These are: the Diagnostic Interview Schedule for Children (DISC) [84, 85], the Children's Interview for Psychiatric Syndromes (ChIPS) [86], the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS-PL; http://www.wpic.pitt.edu/ksads/default.htm; [83, 87], the Diagnostic Interview for Children and Adolescents (DICA[88]; psychometrically weak), the Child and Adolescent Psychiatric Assessment (CAPA) [89], of which young adult and young children versions are available; and the Interview Schedule for Children and Adolescents (ISCA [90]). All interviews are administered by clinicians and include a child/adolescent version and a parent version. In general, children seem to be better informants in describing internalising disorders, and adults (parents, teachers) more reliably describe externalising disorders [83]. The ISCA and the CAPA also explore on DSM-IV axis II diagnoses. Inter-rater reliability appears to be good for the 6 instruments, with kappa's ranging from 0.5 to 1. Overall, the K-SADS-PL has the best test–retest reliability [91] and is mostly used across countries, but takes somewhat lengthy interviewing (between 1 and 3 h).

Notably, in adults, no structured interviews are available that include the full range of disorders of infancy, childhood and adolescence including tic disorders. The most used instruments to assess other comorbid disorders are the Structured Clinical Interview on DSM-IV axis I disorders including the TR form (SCID-I [47, 92]; between 1 and 2.5 h), and the Mini International Neuropsychiatric Interview (MINI), which is an abbreviated version of the SCID-I and takes between 30 min and 1 h to complete [93]. Both the SCID-I and the MINI require training.

Specific evaluation

Clinical interview

Age of onset of first tics should be recorded, as well as tic history and course and age at worst tic severity. Further, inquiries are made about which tics (or comorbid conditions) are considered to be most debilitating, and about their physical consequences (including pain/injury of muscles and joints), about somatosensory phenomena accompanying the tics, tic suppressibility and about exacerbating or relieving factors accompanying the tics (e.g. stress sensitivity). Patients and parents are asked about any possible relationship between infections (throat, ear) and tic exacerbation, to determine whether streptococcal autoimmunity could be a factor (e.g. in relation to Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) [94]). Patients and family members are questioned about the circadian profile of tic activity (including during sleep), to clarify the psychosocial impact of tics on family functioning, learning and quality of life [74]. Finally, the family history should be pinpointed to specific questions about tics, obsessive compulsive and ADHD behaviours in first degree family members.

The clinical examination is accompanied by standardised assessment of tics, comorbid conditions (including ADHD, OCD, self-injurious and anger control behaviours, mood and anxiety, sleep and learning difficulties) and their severity.

Assessment of tics

A considerable difficulty in assessing and quantifying tics is caused by (1) the spontaneous variations of tics in an

individual over time, (2) The large variability in impact of a given level of physical tic severity on an individual or their family and (3) the tendency of patients to suppress their tics, especially when in the office with the clinician. Therefore, it is advisable when assessing tics, to use multi informant data, and to combine direct observation (both at home and in the school/work environment), historical information and—if available—to collect video data, in the clinical setting, 'home alone' or both [95]. Additional videotape tic monitoring might enhance capturing the whole tic repertoire of the patient. Various video protocols have been developed and extensively described, usually advising between 5 and 15 min of videotape recording [95–97].

In general (see Table 5), the evaluation of tics and comorbid symptoms in children and adults is highly comparable, using similar self-report scales and clinician-derived interviews. The differences predominantly lie in the person of the informant. In children this is mostly a parent, in adults the information is obtained—if available—from partner or spouse. In choosing an instrument it is advisable to make a choice based on (1) compatibility of the instrument to international (DSM-IV-TR) criteria; (2) the quality of its psychometric properties and (3) whether it provides scales that are normed across age groups, preferably ranging between infancy and adulthood.

A helpful assessment tool to systematically assess several aspects of the clinical history is of tics is the Diagnostic Confidence Index [98]. The DCI provides a score between 0 and 100 which allows clinicians to measure the likelihood that a person meets criteria of TS. However, validity and reliability criteria are not very well developed.

The most widely used checklists on tic characteristics and severity that combine an observant component and historical information obtained from the patients, parents and or spouses include the YGTSS [69], the Shapiro Tourette SyndromeSeverity Scale (STSSS) [16] and the Hopkins motor and vocal tic scale [99] (for an overview: see Kompoliti and Goetz [100]). The YGTSS includes a clinician-administered inventory of 30 items including 18 categories of motor and vocal tics, self-injurious behaviour and anger control problems to which a severity rating scale has been added. These 10 YGTSS severity items measure the number, frequency, intensity, complexity and interference of motor and phonic tics, and a separate impairment rating on 0–4 scales for each item [69]. Children and adults can be followed using the severity ratings. The YGTSS has high internal consistency and stability [101], convergent validity with other scales and discriminant validity. Overall, the psychometric properties appear to be better than in other scales. Two disadvantages are that time needed to collect information is up to 20 min and the use of the scale needs some training [100].

The STSSS is developed for clinical trials, encompasses five items including the noticeability to others, and interference of daily life due to tics [102]. The STSS is short, easy to use and reliable with high internal consistency. A limitation is that it does not assess tic characteristics. The Hopkins motor and vocal tic scale focuses both on tics and their impairments, using visual analogue scales on which physicians and parents separately rank motor and vocal tics. Three scores are obtained: a total score, a parent (or partner)-derived score and a rater score. Interrater reliability to evaluate tic severity is equally well as seen in the YGTSS, STSSS and CGI [99].

Assessment of comorbid conditions

Recommendations are given to assess the most prevalent comorbid conditions, i.e ADHD and OCD. For recommendations on other comorbidities, we refer to Table 4.

ADHD

To establish the presence and severity of comorbid ADHD, both in children, adolescents and adults, several rating scales can be used to screen on presence of ADHD. However, these scales can only be used as an aid to help diagnosing using standard interviews. With respect to interviews used, assessments should contain key questions for parents (of both children and adults; [103]) on present as well as past performance (starting before age 7) with respect to inattention, impulsivity and hyperactivity. In children, various well validated instruments are used, a.o. the Kiddie-SADS, and the DICA (see here-above). In adults, the picture is less clear, and various interviews, mainly based on DSM-IV criteria of ADHD, have been developed across countries [104]. The particular challenge in assessment of adults lies in the gathering of reliable information on behaviour that has started before age 7 to establish an ADHD diagnosis. This can be extremely difficult, particularly if no informants (parents, older siblings or other family members) are available to provide information on childhood behaviour, and when current comorbid depressive or other psychiatric symptoms hamper reliable information provided by the patient.

ADHD rating scales that are mostly used in children are: the Swanson, Nolan and Pelham questionnaire, 4th edition (SNAP-IV) [105] and the Children's version of the Connors ADHD Rating Scale (CAARS) [106, 107]. The SNAP-IV encompasses a 30 item validated self-report questionnaire with ratings between 0 and 4 per item. Internal consistency, interrater reliability and validity are good. The CAARS (66 item or 30 item versions) has a children's and an adult version and encompasses several subscales with ratings

Table 4 Features of tic disorders versus stereotypies

Feature	Tics	Stereotypies
Age at onset (years)	6–7	<2
Pattern	Variable	Fixed, identical, foreseeable
Movement	Blinking, grimassing, warping, jerking	Arm-hands, wavelike, fluttering, jiggling
Rhythm	Quick, sudden, aimless, but not rhythmic	Rhythmic
Duration	Intermittent, short, abrupt	Intermittent, repeated, prolonged
Pre-movement sensorimotor phenomena	Yes	No
Trigger	Excitement, stress	Excitement, stress, also in case of demands
Suppressibility	Self-directed, short (associated with increased inner pressure)	By external distraction, seldom conscious effort
Family history	Often positive	Maybe positive
Treatment	Primarily neuroleptics	Rarely responsive to medication

between 0 and 4 per item which measure ADHD symptoms, impulsivity, inattention and hyperactivity domains, and (in the long version) ratings with respect to global psychological functioning and self-esteem. The CAARS has the advantages of being thoroughly validated across different age groups, and is suitable to be filled in by multiple informants. The CAARS displays good internal consistency, interrater reliability and validity [103] but has—in adults—the disadvantage of not inquiring retrospectively, although it inquires on whether symptoms have been present before age 7 and caused distress or impairment. An adult self-report rating scale that meets with the criterion of retrospective inquiry on symptoms is the Wender Utah Rating Scale (WURS) [108].

In conclusion, in children the diagnosis of ADHD is more easy to establish than in adults, where assessments with multiple informants should be combined to establish a diagnosis of ADHD [103].

OCD

Some instruments designed to capture the OCD are suitable as a screener in epidemiological samples, some capture the OCD symptoms in clinical samples and some measure OC severity over time. Reliable screeners are: the OC symptom subscale of the CBCL [109] (as an adult version the OC scale of the YASR [110]), an 8 item screener on OC behaviour, and the SOCS [111], a 7 item screener on presence of OC symptoms, the latter being developed for adolescents between 11 and 18 years. Both screeners have good sensitivity and specificity in general populations of children but specificity is lower in psychiatric populations.

To assess symptoms and severity in clinical samples of children and adults, the Leyton Obsessive Inventory including both adult and children's versions are in use (LOI and LOI-CV; 20 and 11 item versions; yes/no answers and 0–3 answers, respectively) [112–114]. The LOI-CV has a self-report and a parent-derived form, the latter being preferable with respect to sensitivity to pick up OC complaints [115]. Disadvantages are that not all OC symptom domains are captured and that the scores predominantly correspond with compulsion severity and not obsession severity. Further, the Children's Obsessive Compulsive Inventory (CHOCI) has been developed [116], based on Maudsley Obsessive Compulsive Inventory [117] and with severity ratings comparable to the YBOCS severity scale [118]. The CHOCI has 14 symptom items and 6 severity items, and is useful as a severity rater but does not encompass the whole range of OC symptoms.

The most recommendable instruments to use which capture the full range of OC symptoms and assess OC severity in children as well as adults are the Children's Yale-Brown Obsessive–Compulsive Scale; CY-BOCS (in children)/YBOCS (in adults), entailing 58–80 items on symptoms and 10 severity items [118–120]), and the Obsessive–Compulsive Inventory-Child's Version; OCI-CV [121] and the adult version: OCI-R [122, 123]. The YBOCS symptom checklist + severity scale have interviewer-based as well as self-report based versions that are equally well in terms of sensitivity and specificity [124], and in children parent-derived versions are used. The (C)Y-BOCS extensively rates presence or absence of lifetime OC symptoms in four domains, of obsessions and checking, washing and contamination, symmetry/ordering behaviour and hoarding [125, 126]. Further, a 10 item severity rating is added, measuring obsession and compulsion severity separately with respect to: time consumingness, distress, interference, resistance and amount of control over obsessions and compulsions. As an extension,

the Dimensional Y-BOCS (DY-BOCS) has been developed, in which symptom severity is measured separately over each symptom domain and avoidance ratings are added [127]. The YBOCS and DYBOCS scales have good psychometric qualities but are very time consuming; (between 1 and 3 h to assess symptoms). Therefore, as a much shorter alternative, the 18 item Obsessive Compulsive Inventory-revised version (OCI-R) [123] and as a child version, 21 item the OCI-R CV [121] is recommended. The OCI-R/OCI-CV encompass 18–21 items on OC symptoms in six symptom domains including doubting/checking, washing, ordering, hoarding and neutralising, with ratings between 0 and 4. Test–retest reliability, comparability with YBOCS and construct and divergent validity (i.e. higher correlations are found with measures of anxiety than depression) are all well.

Physical examination

A general physical and a specialised neurological examination is mandatory to ensure correct diagnosis and exclude severe or progressive neurological disorders [128]. The necessity for any further investigation is determined at this early diagnostic stage. In practice, the typical features of TS virtually rule out alternative major diagnoses. Atypical features such as apparent adult onset or severe deterioration or progression in symptoms should always lead to detailed consideration and investigation to include EEG and neuro-imaging.

Neurological examination is performed to distinguish tics from other movement disorders, most importantly myoclonic dystonias, some forms of epilepsia and stereotypies. In practice, myoclonus—brief shock-like movements of 'non-functional' muscle groups which are not suppressible and usually do not have an associated urge—are the most difficult movements to distinguish from tics. With the presence of sustained or dynamic abnormal postures, it is useful to enquire about and examine for signs of dystonia. A good technique to identify kinesogenic involuntary movements is to for instance observe the writing of the patients; an individual with a myclonic dystonia will need to steady the pen-holding hand with the other to avoid shock-like movements affecting the manoeuvre. Also, observation of fine motor tasks such as putting the lid on a pen is useful to exacerbate/test for myoclonus. Whilst 'dystonic tics' are well recognised, focal or generalised dystonias should not be mistaken for a tic disorder.

Additional investigation with the aid of MRI scanning or EEG is rarely indicated except in those cases where the presentation is not typical in terms of either the semiology of the movement disorder or the presence of features suggestive of the differential diagnoses mentioned above. Indeed, the more common situation is over-investigation, for instance with EEG in cases where a typical tic disorder is mistaken for epilepsy or myoclonus. It is worthwhile seeking expert opinion if doubt exists about the extent of investigation to pursue. Certain neurological conditions can be associated with tic-like movements (Table 4). It is usually straightforward to differentiate these conditions with a thorough history and examination.

The physical examination includes careful examination for dysmorphic features to identify any indication of genetic syndromes. Unusual features may prompt specific genetic testing by consulting a clinical geneticist. Further, in the presence of additional learning difficulties or autism spectrum diagnosis it might be advisable to consult a clinical geneticist as well, as in some cases this high resolution array might reveal a rare genetic aetiology of these heterogeneous disorders.

Neuropsychological profile and assessment

Recent research has provided new insights into the neuropsychological profile of children with TS, mainly through direct comparisons between patients with comorbid ADHD, or, to a lesser extent, OCD, and patients with 'uncomplicated' TS, which represents a minority of the clinical population of children with TS. Although the majority of studies indicate that only TS patients with comorbid conditions exhibit cognitive dysfunction on standardised tests, the actual impact of having TS upon social and academic achievement, quality of life and the overall disability burden of the different subgroups of TS requires further study. For this reason, the prognostic value, and, as a consequence, clinical usefulness of formal neuropsychological testing in children with TS has not been clearly established to date, and most neuropsychometric tools seem appropriate, at present, only in research settings. However, it is useful to summarise the findings on cognitive performance in different subgroups of children with TS, and to identify tests that hold promise for standardised neuropsychometric assessment. Table 5 provides an overview of the test batteries suggested from published studies and more ecologically applicable screens (Fig. 1)..

Patients with 'uncomplicated' TS show barely any impairment on all the main areas of cognitive functioning [129–132]. It should also be noted that no ecologically valid measure of manual speed or dexterity (e.g. typing) has been evaluated in children with TS that shows practically relevant results. Of note, enhanced cognitive function has been identified on tasks of response inhibition in TS patients, with children with 'uncomplicated' TS showing enhanced cognitive control on an oculomotor switching task [133]. Authors suggest that this heightened ability to

Table 5 Tic and comorbidity assessment in children and adults

Topic	Measurement instrument children	Measurement instrument adults	Time
Demographics	Age, sex, education level child and parents, work status parents, ethnicity child and parents (based on country of origin info), marital status parents	Age, sex, education level, work status, ethnicity patient and parents (based on country of origin info), marital status	Max 20
Age at onset tics, OCD, ADHD	Age at onset, age at worst ever	Age at onset, age at worst ever	Max 10
Family history tics/OCD/ADHD	Family tree including disease in family members	Family tree including disease in family members	Max 20
Tic diagnosis according to DSM	Interview (derived from DCI or parts of DISC)	Interview (derived from DCI)	Max 10
Other DSM diagnoses	Kiddie-SADS-PL	MINI/SCID	Max 60
Tic symptoms (past/present)	Y-GTSS (36 items)	Y-GTSS (36 items)	Max 30
OCD symptoms (past/present)	CY-BOCS	Y-BOCS/D-YBOCS	Max 30
ADHD	SNAP/CAARS (parent/teacher/selfrating)	SNAP/CAARS	Max 20
Autism symptoms	Social Responsiveness Scale (SRS)	Autism Questionnaire	Max 25
Impulsive behaviour	BIS 11	BIS 11	Max 5
Sensory premonitory urges	PUTS (10 items)	PUTS (10 items)	
Course of psychopathology			
Severity-tics	Y-GTSS (2 × 10 items; current & worst ever; age at worst ever)	Y-GTSS (2 × 10 items; current & worst ever; age at worst ever)	Max 15
Severity OC symptoms	CY-BOCS severity (2 × 10 items; current & worst ever)	Y-BOCS severity (2 × 10 items; current & worst ever)	Max 10
Severity depression & anxiety	RCADS (47 items)	BDI/BAI (42 items)	Max 20
Psychosocial functioning	CGI	CGI	Max 2
	GTS-QOL (28 items)	GTS-QOL (28 items)	Max 15
Life events	Brugha (29 items)	Brugha (29 items)	Max 15
Estimation of patients' time for the specific baseline measurements	Max 130		Max 125
	Max 175		Max 165

Brugha list of threatening experiences [153]; *DCI* Diagnostic Confidence Index [98], *DISC* Diagnostic Interview Schedule for Children [84, 85], *Kiddie-SADS-PL* Schedule for Affective Disorders and Schizophrenia for School-Age Children (http://www.wpic.pitt.edu/ksads/default.htm) [83, 87], *SCID* Structured Clinical Interview on DSM-IV axis I disorders [47, 92], *MINI* Mini International Neuropsychiatric Interview [93], *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale [119], *Y-BOCS* Yale-Brown Obsessive Compulsive Scale [118, 120], *DY-BOCS* Dimensional Yale-Brown Obsessive–Compulsive Scale [127]; SNAP-IV = Swanson, Nolan and Pelham questionnaire, 4th edition [105]; CAARS = Children's version of the Connors ADHD Rating Scale [106]; SRS = Social Responsiveness Scale [154]; BIS = Barratt Impulsivity Scale [155]; PUTS = Premonitory Urge Tics Scale [156]; Y-GTSS = Yale Global Tic Severity Scale [69]; RCADS = [157]; BDI = Beck Depression Inventory-II [158]; BAI = Beck Anxiety Inventory [159]; CGI = Clinical Global Impression [71]; GTS-QOL = Gilles de la Tourette Syndrome–Quality of Life Scale [76]

control inhibition may be a result of tic suppression over time. This finding needs confirmation in subsequent studies. In sum, based on current evidence, no specific clinical neuropsychological assessment is advised in children with 'uncomplicated' TS.

A body of evidence suggests that the main comorbid conditions, ADHD and OCD, have a detrimental influence on the cognitive performance of children with TS [134].

Children with TS + ADHD exhibit cognitive dysfunction. The main negative impact on cognitive performance seems determined by ADHD, independent of the coexisting tic disorder [131]. This might explain why comorbid ADHD is the main predictor of poorer psychosocial health [135, 136] and the main determinant of the burden of disability [137] in TS patients. However, it is unclear how much of the negative effects of ADHD on disability and social/academic functioning in TS patients is caused by ADHD-related intellectual dysfunction. ADHD comorbidity seems to impact on the general intellectual function of children with TS, as the majority of reports suggest that a lower Full-Scale IQ is accounted for by the presence of the comorbidity [138–140]. Moreover, learning disabilities and other problems concerning academic achievement are estimated to occur in approximately 23% of children with a diagnosis of TS and appear to be highly influenced by coexisting ADHD [140, 141]. Specifically, numerical skills [140] and written language [134] have been highlighted as prevalent in TS.

The performance on manual dexterity (Purdue Pegboard test) or visual-motor integration (Beery Visual-Motor

Integration test) tasks does not differ significantly between patients with TS + ADHD and 'uncomplicated' GTS [132, 142, 143]. In line with children with ADHD only, children with TS + ADHD have been demonstrated to show marked impairment on visual attention (e.g. the Trail Making Test [144]) and sustained attention (Continuous Performance Tests; [132, 145]). Other cognitive domains in which children with TS + ADHD show impairments, compared to patients with 'uncomplicated' TS, are: planning skills [142, 146], response inhibition [131, 147, 148] and cognitive flexibility/set shifting [35, 148, 149]. The meaning of these cognitive impairments to predict outcome in children with TS remains inconclusive. However, the neuropsychological tests described here-above may provide clinically useful additional information on the cognitive profile of children with TS + ADHD.

There is very limited evidence on the neuropsychological profile of children with TS + OCD. It is unclear whether this comorbidity is associated with selective cognitive impairment in children with TS. The cognitive profile of OCD appears to be one of the primary executive dysfunctions, mainly affecting response inhibition and cognitive flexibility [150]. Although memory may be affected as well, these deficits are thought to be secondary to a failure of organisational strategies during encoding [150]. In line with this, patients with TS + OCD demonstrate executive function deficits primarily in response inhibition [151] and set shifting paradigms [152]. As underscored for the other two TS subgroups, information is lacking on the prognostic indicators of this dysfunction on social, academic and psychological wellbeing in children with TS + OCD. For TS + OCD patients, a neuropsychological assessment focused on executive function, primarily response inhibition and cognitive flexibility, may be clinically indicated.

To conclude, in children who are diagnosed with TS in combination with comorbid ADHD or OCD should undergo neuropsychological evaluation encompassing intellectual function, academic attainments, motor skills, attention, executive function and memory. Neuropsychological tests of certain test-batteries with good psychometric properties for the country in question are suggested from published studies and more ecologically applicable screens.

Conclusion

Tic disorders represent a wide range of tics and co-existing symptoms with a varied and heterogeneous presentation. In this guideline, we have recommended a broad range of assessments and investigations to capture the tic/TS phenotype, taking developmental issues into account. In our opinion, it is highly advisable to choose instruments that cover the whole age range between infancy and adulthood, so that the time course of symptoms across ages and life stages can adequately be captured. In most situations, a standard interview with a few additional questionnaires and rating scales are sufficient to guide diagnosis and treatment. However, psychiatric comorbidity occurs in more than three quarters of cases that are referred for specialised care. Further, in a minority of cases a more extensive neurological and psychiatric screen is necessary to differentiate tics from other hyperkinetic disorders and from psychogenic disorders. Finally, neuropsychological assessment can be useful because of the high concurrence of tics with learning disorders, especially in children who have not yet finished education or professional training.

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Appendix

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European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment

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Abstract To develop a European guideline on pharmacologic treatment of Tourette syndrome (TS) the available literature was thoroughly screened and extensively discussed by a working group of the European Society for the Study of Tourette syndrome (ESSTS). Although there are many more studies on pharmacotherapy of TS than on behavioral treatment options, only a limited number of studies meets rigorous quality criteria. Therefore, we have devised a two-stage approach. First, we present the highest level of evidence by reporting the findings of existing Cochrane reviews in this field. Subsequently, we provide the first comprehensive overview of all reports on pharmacological treatment options for TS through a MEDLINE, PubMed, and EMBASE search for all studies that document the effect of pharmacological treatment of TS and other tic disorders between 1970 and November 2010. We present a summary of the current consensus on pharmacological treatment options for TS in Europe to guide the clinician in daily practice. This summary is, however, rather a status quo of a clinically helpful but merely low evidence

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guideline, mainly driven by expert experience and opinion, since rigorous experimental studies are scarce.

Keywords Tics · Tourette · Pharmacologic · Treatment · Guidelines

Introduction

Tic disorders including Tourette syndrome (TS) are neuropsychiatric disorders with higher prevalence rates than previously thought, of up to 3–4% for chronic motor or vocal tic disorders and 1% (range 0.05–3%) for TS [196], which is the combination of chronic motor and vocal tics persisting for at least one year. The typical age of onset of tics is between 4 and 8, and tics reach their peak severity early in the second decade of life often followed by a time of remission of tics [44, 228]. Overall, TS has often a favorable prognosis: follow-up studies of TS suggest that approximately one third of children with TS are essentially symptom-free as adults; another third will have mild tics that do not require clinical attention [22]. Adults who still have symptoms severe enough to come to clinical attention are therefore unusual representatives of all subjects who have received a diagnosis of TS.

Diagnosing a tic disorder including the differentiation of tics from other movement disorders is usually a simple task (see Cath et al. this issue). It is, however, essential to detect coexisting conditions and to assess the contribution of the tics and/or coexisting conditions to the patient's psychosocial impairment in everyday life, because the coexisting conditions often are closely related to the latter, yet they do not explain fully the level of function [95].

Indications for treatment of TS

We use the term TS in these guidelines, although information also applies to other chronic tic disorders. Decisions about treatment of TS must be based on a thorough and broad diagnostic process. It is difficult to give guidelines with regard to indications for pharmacological treatment of TS, first, because persons with TS have a high interindividual variability of symptoms, secondly, due to the temporal fluctuations of tics and thirdly, because coexisting conditions may interfere with the treatment effects for the tics. Moreover, subjective impairment does not necessarily equate objective tic severity: some individuals with relatively severe tics experience only mild impairment, whereas in other cases mild tics may be associated with significant suffering [225].

Many children and adolescents with TS do not require treatment for their tics, since their tics do not interfere with daily life or recreational activities. Indeed, only a minority of individuals with tics seek medical advice [194]. Many patients do well with a *watch and wait strategy* after psychoeducation and reassurance. Psychoeducation in TS has the aim to improve the tolerance for symptoms and to support stress reduction. Psychoeducation includes information about the long- and short-term variability of tics, about the natural course and about possible coexisting problems. A *watch and wait* strategy is also justified by the fact that we still lack evidence of the effect that pharmacological treatment of TS has on the natural long-term course and hence on the prognosis of the disorder and how this kind of treatment may influence the natural course of brain development. All pharmacological treatment options are therefore mere symptomatic treatment that alleviate, but do not cure the tics [87].

Non-pharmacologic and/or pharmacologic interventions should be considered in addition to psychoeducation for persons with clear impairment associated with the tics, either at first referral or later, due to exacerbation of symptoms. A number of reviews (e.g. [87, 246]) have published lists of indications for pharmacological treatment of tics, but none of them reflects the consensus of experts. We recommend that treatment of tics should be considered in the following circumstances, especially when persisting for some days.

Tics cause subjective discomfort (e.g. pain or injury)

Pain in TS may arise from the actual performance of frequent or intense tics causing discomfort by sudden or repeated extreme exertion (e.g. with head or neck). This kind of pain is usually musculoskeletal, although rare examples of neuropathic pain may occur. Tics can, in rare cases, cause injuries [125], e.g., a fracture line of both peroneal bones in a 13-year-old boy with TS and obsessive–compulsive disorder (OCD) admitted to hospital because of pain in his legs [80]. Striking or being struck by a moving body part involved in large amplitude tics may also cause pain and is sometimes difficult to distinguish from deliberate self-injury. Additionally, some patients obtain relief from tics while experiencing pain, to such an extent that they will deliberately provoke pain to obtain benefit [193]. A smaller number of patients complain of pain associated with the irresistible urge to tic or with aggravating premonitory urges during voluntary efforts to suppress their tics. Some patients report that tics worsen their headaches or migraines. In those cases, tic-suppressive medication could be helpful in reducing the use of pain medication and should be considered.

Tics cause sustained social problems for the patient (e.g., social isolation or bullying)

Persistent complex motor tics and loud phonic tics can cause social problems. Tics may cause isolation, bullying, or social stigmatization; loud phonic tics may result in the child being put out of the classroom. In such cases, a tic reduction, in addition to psychoeducation for the teacher, can be socially very helpful.

However, tics do not lead to social impairments in all cases. Therefore, the issue of social problems needs to be assessed carefully. For example, parents of young children are often exceedingly worried about social problems, whereas adolescents sometimes overestimate the social consequences of their tics and children in the first elementary grades are often tolerant of tics. Coexisting conditions are more often the cause than tics, if a primary school child gets socially isolated by peers [54]. In higher school classes, bullying and social stigmatization due to tics becomes more common. After proper psychoeducation, many children and adolescents will accept their tic symptoms and await the natural remission; however, sometimes medication is indicated to avoid social stigmatization.

Tics cause social and emotional problems for the patient (e.g., reactive depressive symptoms)

In addition to the aforementioned, sustained social problems, consequent to negative reactions of the social environment, some patients develop depressive and anxious symptoms, low self-esteem, and/or social withdrawal. In those cases, it is not fully clear as to what extent coexisting (sub)clinical symptomatology and self-triggered reactions cause the patients social and emotional reactions to his/her tics.

Tics cause functional interference (e.g., impairment of academic achievements)

Functional interference due to tics is relatively rare [87]. However, especially homework and falling asleep can be prolonged by bouts of tics and sleep may be disturbed followed by hypoarousal during daytime. Frequent phonic tics can impair fluency of speech and thus conversations. Moreover, children can expend mental energy in the classroom to suppress their tics, thus reducing their attention to schoolwork and interfering with their academic performance [130].

Pharmacological treatment options for TS

Pharmacotherapy has probably the fastest onset when compared with behavioral treatment options but this clinical experience has never been tested in a clinical trial. The same holds true for the efficacy of tic reduction.

Genetic studies have so far not succeeded in pinpointing a clear deviation in the biochemical pathways in patients with TS. The existing models are mainly based on the efficacy of medication rather than on rigorous and replicable models. Findings from clinical medication studies, as well as from imaging studies and human material from blood, urine, cerebrospinal fluid, and postmortem brain tissue analyses in rather small samples led to the common hypotheses on neurochemical deviances in TS [97]. Although evidence is appealing for deviances in the dopaminergic system, other imbalances, such as in the serotoninergic, noradrenergic, glutamatergic, Gamma-aminobutyric acid (GABA)-ergic, cholinergic, and opioid metabolism in TS [97, 267] seem probable. Moreover, evidence grows that those systems play interactively together, especially the dopaminergic [263] and the serotonergic [160] system.

Studies supporting the strong hypothesis of an imbalance in the dopaminergic system have shown an increased number of striatal [285] and cortical [157, 290] dopamine receptors, as well as differences in binding to dopamine transporters in the basal ganglia [42, 233, 249, 286, 287] and release of dopamine following stimulant application [250]. Therefore, modulating the dopaminergic metabolism (particularly by blocking the post-synaptic D2-receptors) is the main action of drugs used in the pharmacologic treatment of tics.

Given that only a limited number of studies on pharmacological treatment options for TS met rigorous quality criteria, we have devised a two-stage approach. First, we present the highest level of evidence by reporting the findings of existing Cochrane reviews in this field. Subsequently, we provide the first comprehensive overview of all reports on pharmacological treatment options for TS through a MEDLINE, PubMed, and EMBASE search for all studies that document the effect of pharmacological treatment of TS and other tic disorders between 1970 and November 2010. We found additional studies by going through references of each article. Given the scarcity of well-designed and well-powered studies, we think it is timely to provide such a complete overview of all available studies in order to present all facets of pharmacologic treatment accumulated over the past decades. Finally, we present a summary of the current consensus on pharmacological treatment options for TS in Europe to guide the clinician in daily practice. This summary is, however, rather a status quo combined with a clinically helpful but merely low evidence guideline and is mainly driven by expert experience and opinion, since rigorous experimental studies which would allow to better guide through well based clinical evidence are scarce.

We do not grade the studies with respect to their quality and include all available studies in view of the small base of evidence of pharmacological treatment options for TS. We present all existing studies for the different pharmacological agents, with respect to their effects on tics and other accompanying symptoms and adverse reactions or interactions with other agents.

Cochrane reviews

Although broad clinical experience guides the pharmacologic treatment of tics, the actual evidence based on randomized controlled trials (RCT) is alarmingly limited. Therefore, it is not surprising that all three existing Cochrane reviews on the pharmacologic treatment of tics in TS [51, 186, 189] came to the same conclusion, i.e., that the evidence for efficacy and safety of the studied drugs does not allow firm recommendations.

Pringsheim et al. [189] included six randomized controlled trials on pimozide in TS (total 162 participants, age range 7–53 years). Pimozide was compared to placebo and haloperidol (two trials), placebo (one trial), haloperidol (one trial), and risperidone (two trials). In summary, the six studies showed that pimozide was more effective than placebo in reducing tics. It was slightly less effective than haloperidol but showed fewer adverse reactions. The two studies that compared pimozide and risperidone revealed no important differences between these medicines for either reduction of tics or adverse reactions.

A more recent Cochrane review searched for all randomized, controlled, double-blind studies comparing atypical antipsychotics with placebo for the treatment of tics in TS [186]. However, it did not include the two above-mentioned trials because both the studies compared the atypical agent, risperidone, with an active treatment modality, without a control group that received placebo medicine. Parallel-group and crossover studies of children or adults, at any dose and for any duration, were screened. Only three randomized placebo-controlled trials, two involving risperidone and one involving ziprasidone were thus identified. Risperidone was superior to placebo in one trial although the 95% confidence intervals were large. Two trials did not detect a statistically significant difference between treatment with risperidone and with ziprasidone against placebo. Risperidone caused several extrapyramidal adverse reactions and weight gain.

The third Cochrane review on the pharmacological treatment of TS [51] analyzed the effect of Delta 9-tetrahydrocannabinol (Delta 9-THC). A total of 28 different patients included in one double blind, crossover trial and in one double blind, parallel group trial were studied. Although both trials reported a positive effect of Delta 9-THC, the improvements in tic frequency and severity were small and only apparent on selected outcome measures.

In summary, all three available Cochrane reviews urgently advocate for future trials with longer durations and larger groups to investigate the safety and efficacy of pharmacological treatment in TS. Future trials should also use the Yale Global Tic Severity Scale (YGTSS) as primary outcome measure and standardized rating scales of adverse effects, e.g. the Extrapyramidal Symptom Rating Scale (ESRS).

Complete review

Antipsychotic agents

Positive effects for D2 dopamine receptor blockers have been reported in the treatment of tics since 40 years (in average a marked decrease of tics in about 70% of cases [237]). Particularly, the blockade of striatal D2 dopamine receptors is thought to lead to reduction of tics. However, a high blockade of the receptors correlates also with the rate of unfavorable adverse reactions, such as extrapyramidal symptoms (EPS) or tardive dyskinesia (TD) [27].

Typical antipsychotics For a long time, placebo-controlled treatment studies in TS have been conducted only to prove the efficacy of the typical antipsychotics, *haloperidol* and *pimozide*. In an early randomized, double-blind, placebo-controlled crossover study, both pimozide and haloperidol significantly decreased tic frequency in nine patients with TS [206]. The results of a subsequent randomized, double-blind, placebo-controlled study of the treatment of 57 patients with TS confirmed that both haloperidol and pimozide were more effective than placebo, but haloperidol was slightly more effective than pimozide. Adverse reactions occurred more frequently with haloperidol versus placebo, but the frequency was not significantly different for haloperidol as compared with pimozide [236]. The dosages used in this study ranged from 2 to 20 mg/day for haloperidol and from 2 to 48 mg/day for pimozide. The effect of the medicine with a strong blockade of D2 dopamine receptors reduced tics in up to 80% of the cases [236]. However, in daily clinical practice, lower doses such as 1–4 mg/day for haloperidol and 2–8 mg/day for pimozide are typically used nowadays to treat TS [128, 191, 224].

In a double-blind, 24-week, placebo-controlled, randomized, double-crossover study of more commonly used doses of haloperidol (mean of 3.5 mg/day) and pimozide (mean of 3.4 mg/day) conducted with 22 subjects, aged 7–16 years, pimozide was significantly more effective than placebo in reducing tics, whereas haloperidol failed to have a significant effect. Moreover, haloperidol exhibited a threefold higher frequency of serious adverse reactions and significantly greater extrapyramidal symptoms relative to pimozide [214]. In contrast to several other studies,

haloperidol was not superior to placebo, possibly due to the limited study power.

Furthermore, a long-term naturalistic follow-up study (1–15 years) of 33 TS patients treated with pimozide (2–18 mg) or haloperidol (2–15 mg) suggested benefits of pimozide over haloperidol; both drugs produced comparable relief of symptoms at follow-up; significantly, more patients on haloperidol (8 of 17) as compared with those on pimozide (1 of 13) discontinued treatment [218]. In addition, haloperidol produced significantly more acute dyskinesia/dystonia than pimozide.

A third typical antipsychotic, *fluphenazine,* has been used particularly in the United States for many years to treat TS, though it has merely been studied systematically. In an open-label study that included both children and adults, fluphenazine was effective at doses ranging from 2 to 15 mg/day in 17 of 21 patients [91]. In a naturalistic follow-up of 41 patients, treatment with fluphenazine for at least 1 year was safe and effective [240]. A small controlled study of fluphenazine, trifluoperazine, and haloperidol found similar reduction of tics. However, fluphenazine was better tolerated [25]; haloperidol was associated with more sedation and extrapyramidal adverse reactions.

The high frequency of drowsiness and extrapyramidal-motoric adverse reactions (dystonia, akathisia, pseudo-Parkinsonism, probably due to the strong dopaminergic blockade in the nigrostriatal pathways) limits the use of the typical antipsychotics foremost in higher doses. It has also been reported that akathisia due to antipsychotic agents may worsen the tic symptoms [280]. Moreover, several case reports raised concerns about the risk of treatment with typical antipsychotics to induce tardive dyskinesia [93, 192, 241]. Although, it is difficult to confidently quantify the rates of tardive dyskinesia owing to the limited long-term data available, the risk of this potentially debilitating and treatment-persistent adverse reaction ought to be considered in the choice of treatment [284]. This is important with greater certainty as atypical antipsychotics have shown a significantly lower risk of tardive dyskinesia [155].

Other adverse reactions, e.g., the onset of anxiety [29, 138, 154] or hyperprolactinemia with its adverse reactions, such as gynecomastia, galactorrhea, irregular menses, and sexual dysfunction [205] are more common adverse reactions than tardive dyskinesia. Additionally, during long-term medication with haloperidol, the increased appetite may result in significant weight gain [114].

Benzamides The benzamides (*tiapride*, *sulpiride, and amisulpride*) are further selective D2 dopamine receptor antagonists but in contrast to the typical antipsychotics with low (sulpiride) or as good as no (tiapride) antipsychotic action.

In addition to tiapride binding to the supersensitive D2 dopamine receptors in the ventral striatum and parts of the limbic system (Locus coeruleus), a blockade of some serotonergic receptors (5HT3, 5HT4) is assumed. Since the 1970s, there have been reports about successful treatment of TS with *tiapride* [61, 124, 139, 145, 183]. Several placebo-controlled studies on small sample sizes followed [43, 74]. Only one randomized, double-blind, placebo-controlled crossover study has been published with tiapride (involving 17 children), indicating a significant reduction of tic symptomatology [68]. The main adverse reactions were drowsiness, moderate transient hyperprolactinemia, and weight gain (the maximum was 10 kg during 18 months in two children). Such massive weight gain is rather the exception than the rule, because the mean weight gain was 2–4 kg [151] with the dosage range of 100–900 mg/day. Tiapride had no adverse reactions on children's cognitive performance. Neither neurophysiological parameters such as the EEG frequency analysis and sensory-evoked potentials were affected by tiapride nor were the neurosecretory, hypothalamic-hypophyseal regulation of the sex hormones, thyroid stimulating hormone, growth hormone, or thyroid hormone impaired. This rather advantageous profile of short- and long-term adverse reactions with doses effectively reducing tics has been proven in rats too [23, 227].

Since 1970 [291], the positive effects on tics have also been reported regularly for the benzamide *sulpiride* [199]. It is a highly selective D2-dopamine receptor antagonist associated with less extrapyramidal and vegetative adverse reactions than haloperidol [156]. An ongoing discussion focuses on whether that medication possibly has a specific binding in mesolimbic and mesocortical systems. In addition to its mild antipsychotic potency, it has some antidepressant effect in low doses (in particular 50–200 mg daily) as well as a stimulating and anxiolytic effect [176]. In an open-label retrospective review in which 63 out of 114 patients (55%) suffering from TS had been treated with sulpiride [197], worthwhile beneficial effects occurred in 37 patients (59%). In a 14-week, randomized, double-blind, placebo-controlled crossover study trial of fluvoxamine (a specific 5HT reuptake inhibitor) versus sulpiride followed by single-blind combined therapy (4 weeks) in 11 subjects with coexisting obsessive–compulsive disorder and TS [85], sulpiride monotherapy reduced tics and non-significantly improved obsessive–compulsive symptoms. Fluvoxamine, either alone or combined with sulpiride, non-significantly ameliorated tics and reduced obsessive–compulsive symptoms. Just recently in an open-label study with 189 children and adolescents with an average age of 8 years (range 3–15 years), 6 weeks' treatment with sulpiride improved motor as well as vocal tics. The most commonly encountered adverse reaction was sedation

(reported by 16.4%) [100]. Furthermore, in patients suffering from OCD without tics, sulpiride has proven its efficacy [14, 270]. In one case of treating TS with the combination of sulpiride and imipramine, the tics increased [69]. This might be attributed most likely to the reported effects of increase of serotonin associated with increase of tics.

The main adverse reactions of sulpiride treatment are sustained sedation or drowsiness (up to 25%) and, less frequently, depression, despite its antidepressant, drive-normalizing, and mood-brightening potential [197]. Patients have also complained about restlessness and sleep disturbances [209]. Another important problem with sulpiride is a strong stimulation of prolactin-secretion causing galactorrhea/amenorrhea and a commonly observed increased appetite leading to weight gain [12, 105, 281]. Other adverse reactions occur less frequently (hypotension, rarely long-QT syndrome, dry mouth, sweating, nausea, activation or sedation, insomnia, allergic rash, or pruritus). There has only been one case report about tardive dyskinesia in an adult treated with sulpiride for tics (Eapen, Katona et al. 1993).

Successful treatment of TS disorder with *amisulpride* has been published only in case reports [75, 272].

Atypical antipsychotics Atypical antipsychotics are effective in the treatment of TS too. The best evidence is available for risperidone. We will herein review all atypical antipsychotics in the order of their date of FDA approval for non-TS disorders.

Clozapine, a dibenzodiazepine with 5-HT2A, 5-HT2C, 5-HT3, and weaker D1 antagonist properties, and the first FDA-approved atypical antipsychotic agent (FDA approval: 1990), has not been found to be helpful in the treatment of TS in several case reports which also documented the serious adverse reactions associated with this agent [35]. On the contrary, it is reported that clozapine exacerbates tics [13] and induces stuttering, facial tics, and myoclonic seizures [15].

The atypical antipsychotic agent best studied for the treatment of TS is *risperidone* (FDA approval: 1993) with a high affinity for dopamine D2- and 5-HT2-receptors. However, in several case reports and open-label studies including small groups of patients, risperidone showed similar efficacy across different ages as haloperidol and pimozide did with less frequent and less severe adverse reactions [30, 58, 86, 122, 140, 198, 219, 238, 261, 275]. The efficacy of risperidone has been confirmed in two randomized, double-blind, placebo-controlled trials involving 26 children and 8 adults with an age range 6–62 years [226], and 48 adolescents and adults between 14 and 49 years, [60], respectively, with mean daily doses of about 2.5 mg (range 1–6 mg/day). Gaffney et al. subsequently [83] compared 8 weeks' treatment effects of risperidone with clonidine in 21 subjects with TS aged 7 to 17 years in a randomized, double-blind study. Risperidone and clonidine appeared equally effective in the treatment of tics; however, in the cases with comorbid obsessive–compulsive symptoms, risperidone was superior. The most common adverse reaction seen with both treatments was mild-to-moderate sedation, which subsequently resolved with continued administration of the medication or with a dose reduction. No clinically significant extrapyramidal symptoms were observed.

Furthermore, in a 12-week, randomized, double blind, parallel group study, both risperidone (26 patients were treated with a mean daily dose of 3.8 mg) and pimozide (24 patients were treated with a mean daily dose of 2.9 mg) reduced tics, anxiety, and depressive mood [28], whereas obsessive–compulsive symptoms improved only in the risperidone group. The latter finding is in line with the superior efficacy of risperidone for coexisting obsessive–compulsive symptoms in TS in the study of Gaffney et al. [83] as well as in an earlier case report [86]. Although the severity of extrapyramidal adverse reactions was low in both the groups, fewer patients in the risperidone group reported extrapyramidal adverse reactions ($n = 4$) as compared with the pimozide group ($n = 8$). Depression, fatigue, and somnolence were reported as the most prominent adverse reactions in both treatment groups. This is in line with a retrospective study carried out on 58 adult and adolescent TS patients who were treated with risperidone; 17 patients (29.3%) developed a major depressive disorder, including 1 patient who later committed suicide, and 13 patients (22.4%) became dysphoric while taking risperidone [143]. In a randomized, double blind, crossover study of 19 TS children (ages, 7–17 years), who underwent a 4-week treatment with pimozide or risperidone, followed by the alternative treatment after a 2-week placebo washout, risperidone was more effective than pimozide in reducing tics, in contrast to Bruggeman et al.'s report [28], which suggested that risperidone and pimozide were equally efficacious in the treatment of TS.28 Risperidone, however, was associated with more weight gain during the 4-week treatment periods. No serious adverse reactions were reported [88].

Risperidone also appears to be effective in treating aggressive behavior in patients with TS. In a retrospective chart review of 28 children and adolescents (one female) aged 5–18 years with TS and aggression problems, 22 (78.5%) showed both decreased aggression scores and tic reduction when treated with a mean daily dose of 2 mg risperidone [219]. This is in accordance with the potential of risperidone to manage pediatric aggression in other disorders [177]. Moreover, positive effects of risperidone not only on tics but also on sleep disturbances have been reported in the case of a 12-year-old boy with no previous psychopharmacological treatment [7].

Finally, in line with the other agents, the problem of causality between treatment and the natural course of tic symptomatology has also been mentioned for risperidone leading to one report about induction of tics by risperidone [72].

Several case reports [17, 18, 117, 141] and open-label studies [33, 126, 148, 262] have suggested efficacy of *olanzapine* (FDA approval: 1996) in the treatment of TS in adolescents and adults during the last 10–15 years. In four patients with severe TS (aged 19–40 years), a 52-week, double blind, crossover study with olanzapine (5 and 10 mg daily) versus low-dose pimozide (2 and 4 mg daily) was performed [171]. The reduction in tic severity was highly significant with 10 mg olanzapine versus baseline and versus 2 mg pimozide, and was significant for 5 mg olanzapine versus 4 mg pimozide. Only moderate sedation was reported by one patient during olanzapine treatment, whereas three patients complained of minor motor adverse reactions and sedation during pimozide treatment. All patients opted for olanzapine treatment at the end of the study. Compared to other antipsychotics, olanzapine has a greater activity at serotonin 5-HT_2 receptors than at D2 dopamine receptors. This may explain the lack of extrapyramidal effects. Additionally, olanzapine does not appear to block dopamine within the tubero-infundibular tract, explaining the lower incidence of hyperprolactinemia than with typical antipsychotic agents or risperidone. Nevertheless, the most widely reported adverse reactions were drowsiness/sedation and increased appetite frequently followed by weight gain [148]. In this context also metabolic adverse reactions (glucose and lipid metabolism) arise [184], although there seems to be no correlation between weight gain and metabolic disturbances [153].

Quetiapine (FDA approval: 1997) with its greater affinity for 5-HT2 receptors than for dopamine D2 receptors has shown its efficacy in reducing tics in two children with TS [179, 181, 182]. In an open-label trial with 12 subjects with a mean age of 11.4 ±2.4 years quetiapine reduced tics significantly [159]. Three subjects complained of sedation in the first week of treatment, but in the 8 weeks under investigation patients did not experience extrapyramidal adverse reactions and no statistically significant weight gain. Contrarily, in a retrospective study with longer observation period and higher dosage (175.0 SD 116.8 mg/day) of quetiapine the only noteworthy adverse reaction was weight increase. Quetiapine reduced tics also significantly in an open label study of 12 patients aged 8–18 years with TS [48]. Routine laboratory parameters and serum prolactin level were all normal and did not change throughout treatment.

Although there has been great hope for *ziprasidone* (FDA approval: 2001) as a potent treatment option in TS without the problem of weight gain [6], only one randomized, double blind, placebo-controlled study in 28 children and adolescents (7–17 years) [212] and one open open-label study in 24 children and adolescents (7–16 years) so far has proved this expectation [211, 213]. A mean daily dose of 28.2 mg ziprasidone reduced tics more effectively than placebo. Mild transient somnolence was the most common adverse reaction of low-dose exposure (5–20 mg/day), consistent with what is seen in clinical practice. This may be caused by enhanced 5-HT2C antagonistic activity of ziprasidone at low doses [260]. No patient experienced extrapyramidal symptoms, akathisia, or tardive dyskinesia, although administration of a single, low dose of ziprasidone may not be reflective of either higher doses or long-term risk in a naturalistic treatment setting [213]. In addition, there was no weight gain and changes of the analyzed laboratory parameters except of prolactin. Although QT prolongation has been discussed prominently in ziprasidone, a single dose of ziprasidone to treat TS was well tolerated without clinically significant effects on electrocardiograms collected around the time of maximum serum concentration [213] and even in higher doses no elevated risk of QT prolongation has been reported compared to other antipsychotics [266].

In addition to ziprasidone also *aripiprazole* (FDA approval: 2002) induced no weight gain during an 8-week, open-label trial with a flexible dosing strategy of aripiprazole in 72 children and adolescents with TS aged 6–18 years [49]. In a 10 week open-label, flexible-dose study with eleven subjects (10 males) with TS (age 9–19 years) who had not responded to or had not tolerated previous tic medication, effects of aripiprazole were promising [142], albeit with some weight gain in five patients. Finally, in an open-label, flexible-dose study including sixteen children (15 males) aged 8–17 years there was a mean increase of 2.3 kg after a 6-week trial with aripiprazole [167]. It provides a high affinity at dopamine D2 receptors but acts in contrast to other atypical antipsychotics as a partial agonist. Under treatment of clinical useful doses (10–30 mg/day) aripiprazole exhibits D2-receptor binding of 80–100% [96]. However, while binding at the active state of D2-receptors, aripiprazole shows 30% agonistic activity compared to dopamine [34]. Aripiprazole also acts as a partial agonist at 5-HT1A receptors and as a potent antagonist at 5-HT2A receptors [113]. This profile raised the hope that aripiprazole might be superior to previous pharmacological treatment options even in refractory cases. Excellent efficacy in the treatment of tics has been reported in a total of 201 cases, at least 31 of them adults [31, 47, 49, 52, 55, 63, 76, 103, 106, 118, 119, 142, 158, 166, 167, 173, 265, 288, 289]. A randomized, double blind, placebo-controlled study is, however, still lacking. Nevertheless, this drug should be considered because of its promising perspective based on actual clinical experiences. Even in "refractory" TS, aripiprazole has

shown about 75% reduction of severe coprolalia in a 28-year-old man [16] as well as good efficacy in treating TS and coexisting OCD in an adult female [283]. Accordingly, Budman et al. [32] found in their retrospective, observational study of 37 children and adolescents with TS who were refractory to previous treatment that aripiprazole still reduced tics as well as explosive outbursts in these patients. Aripiprazole was tolerated reasonably well, although 8/37 (22%) children discontinued treatment; most common adverse reactions included weight gain, akathisia, and sedation at a mean daily dose of 12.3 (SD 7.50) mg in the 29 subjects who completed the study. In a 12-week, open-label trial with flexible dosing strategy aripiprazole revealed a good tic reduction in 15 participants, aged 7–19 years. Nausea and sedation were the most commonly reported adverse reactions that ameliorated in all participants within 2 weeks, with the exception of 1 participant who had continuously complained of sedation, but did not stop taking the drug [232]. The mean weight gain during this study was negligible.

For the newest atypical antipsychotic *paliperidone* (FDA approval: 2006) as well as for *sertindole* (not approved by the FDA for use in the USA) no data on the treatment of tics have been published.

Noradrenergic agents

In general, noradrenergic agents (clonidine, guanfacine, and atomoxetine) are mostly used in children and adolescents with a combination of attention-deficit/hyperactivity disorder (ADHD) and mild tics given their efficacy in treating ADHD symptoms in addition to tics [11]. Their tic-suppressing effects seem to be generally smaller, however, than those of antipsychotic agents.

Despite the frequent use of the α-2 adrenergic agonist *clonidine* for nearly three decades in the treatment of TS, controlled studies with clonidine are few in number. It is used more commonly in America than in Europe [195]. Case reports of clonidine's efficacy in treating TS appeared in the early 1980s [150] and open-label trial evidence has been contradictory [45, 46, 234, 248]. A single-blind, placebo-controlled trial demonstrated a significant improvement in 6 out of 13 patients [133]. A randomized, placebo-controlled trial on 47 patients (7–48 years old) suffering from TS showed that treatment with clonidine reduced tic severity and frequency better than placebo [134], whereas another randomized, placebo-controlled study in 30 children and adults with TS found no difference [92]. A randomized, double blind, placebo-controlled study of desipramine and clonidine for the treatment of ADHD in TS revealed that clonidine did not alter tic severity in 34 children aged 7–13 years [247]. However, in the largest well-designed, randomized trial on orally administered clonidine, which included a placebo group, clonidine reduced tics significantly [271].

A transdermal clonidine preparation is also available and has been tested for the first time in nine patients in a placebo-controlled crossover trial. Although no objective improvement was recorded, most subjects felt they had improved [84]. A recent randomized, double blind, placebo-controlled multicentre trial using a clonidine adhesive patch revealed in the randomly assigned clonidine group ($n = 326$) a significant improvement of TS in 68.85% compared to 46.85% in the clinical control group ($n = 111$) [62]. Accordingly, clonidine transdermal patch treatment was effective in 53 out of 65 children with TS [116].

Adverse reactions of clonidine include sedation, dry mouth, headache, irritability, and midsleep awakening [62]. Blood pressure and pulse should be measured at baseline and monitored during dose adjustment. Specific guidelines for blood pressure monitoring during follow-up have not been established but regular monitoring of pulse and blood pressure changes, and symptoms suggestive of cardiovascular problems (e.g., exercise intolerance, dizziness, syncope) is recommended [53]. Baseline and follow-up electrocardiograms have been recommended in some practice guidelines [64], but not in others [53]. Although blood pressure is generally not a problem with clonidine, patients and families should be educated about the possibility of rebound hypertension, tics, and anxiety with abrupt discontinuation [19]. Although many authors report that the adverse reactions tend to be mild and transient, this view is not fully supported by others [89, 99, 137] especially when moderate to severe tics require higher dosage.

Guanfacine, another α-2 adrenergic agonist, has modest efficacy in reducing tics and in improving attention in children and adolescents. An open-label study of guanfacine in 10 children with TS [40] and in 25 medication-free children (23 males and 2 females) [24] with TS + ADHD aged 7–16 years revealed a significant decrease in tic severity and improvement in attention. In addition, a case report had described a 6-year-old boy with TS treated successfully with guanfacine [77]. These open label observations were confirmed by a randomized placebo-controlled double-blind trial in 34 children with TS + ADHD with a mean age of 10.4 years [223]. In contrast, in another double blind, placebo-controlled study on 24 children with TS aged 6–16 years guanfacine was not superior to placebo [50]. In summary, whether guanfacine would be effective for the treatment of moderate to severe tics remains unanswered [225]. In addition, the suggestion that guanfacine is a better tolerated alternative to clonidine remains unclear without a direct comparison study [217].

The most common adverse reactions of guanfacine are somnolence, headache, fatigue, sedation, dizziness,

irritability, upper abdominal pain, and nausea. Somnolence, sedation, and fatigue adverse reactions emerge within the first 2 weeks of dosing and generally remit [210]. There is a concern that guanfacine has a propensity to induce mania in children with a personal or family history of bipolar disorder [102] as well as syncopal episodes probably due to drug-induced hypotension or bradycardia [123]. Guanfacine approved to treat hypertension in several European countries has been withdrawn from the market in several European countries probably due to lack of financial success.

The selective noradrenaline reuptake inhibitor *atomoxetine* had already been shown to be effective in randomized, placebo-controlled trials for treating ADHD in children [41]. Also in the treatment of ADHD with coexisting tics its efficacy was tested in a large, industry-sponsored multicenter study in 148 children [5]. Atomoxetine reduced both tics and ADHD symptoms in the study's subgroup suffering from ADHD + TS [256]. Significant increases of mean pulse rate and rates of treatment-emergent nausea, decreased appetite, and decreased body weight were observed during medication with atomexetine. Concerns were raised, however, that children with severe ADHD or tics might have been unlikely to be enrolled in the study [87] which had a fairly high dropout rate in both treated (34%) and untreated (26%) groups during the double-blind portion of the trial. Moreover, case studies describe patients experiencing manifestation, recurrences, or exacerbation of tics following treatment with atomoxetine [136, 178, 180, 230].

Alternatives

Tetrabenazine, a vesicular monoamine transporter type 2 inhibitor, depletes presynaptic dopamine and serotonin stores and blocks postsynaptic dopamine receptors. In view of the hypothesized supersensitivity of dopaminergic receptors thought to be responsible for the tics in TS [231], tetrabenazine might be an alternative to antipsychotic treatment. Its divergent mechanism of action might result in different efficacy and adverse reactions profiles than the treatment with antipsychotics [109]. In some clinical studies on hyperkinetic movement disorders, including patients or samples with TS, tetrabenazine has shown its potential to ameliorate tics [108, 109, 111, 112, 174, 268, 278]. Results of two retrospective chart reviews enrolling only patients with TS ($n = 77$; mean age about 15 years; [120] and [188]) showed that 18–24 months' treatment with tetrabenazine resulted in a moderate to marked improvement in functioning and TS-related symptoms in over 80% of patients. Adverse reactions included drowsiness/fatigue (36.4%), nausea (10.4%), depression (9.1%), insomnia (7.8%), and akathisia/parkinsonism (6.5%), but these symptoms improved with reduction in dosage [120]. Weight gain was less pronounced in doses of comparable efficacy than under treatment with antipsychotics and most patients who switched from an antipsychotic drug to tetrabenazine subsequently lost weight [170]. There were no reports of tardive dystonia or serious adverse reactions. In contrast there is a report about two patients with TS who developed tardive dystonia after treatment with antipsychotic agents. The dystonic movements persisted after the offending drugs were stopped and improved with tetrabenazine [252]. In summary, these findings encourage to conduct further studies.

Findings from preclinical studies in animals have suggested that *nicotine* might potentiate the effect of antipsychotic agents used to treat TS. Indeed, in 2 case reports negative effects of smoking cessation on TS have been reported [57, 59]. In initial open-label studies, chewing nicotine gum in addition to treatment with antipsychotics reduced tics in frequency and severity and improved concentration and attention [146, 216]. Similar effects were observed in a subsequent controlled trial involving nicotine gum plus haloperidol. Only in the group chewing the nicotine gum, tic frequency was reduced, while placebo gum alone had no effect on tic symptoms [147]. However, the short duration of effects as well as the bitter taste and gastrointestinal adverse reactions limit the compliance. Similar findings have been reported for application of transdermal nicotine patches to potentiate haloperidol in TS [242, 243]. In 11 poor-responders to antipsychotic treatment of TS, transdermal nicotine patches delivering 7 mg of nicotine in 24 h reduced tics 47% in frequency and 34% in severity [244]. In two of these patients tic reduction lasted even after removal of the transdermal nicotine patches. This result was in line with similar reports on tic reduction longer than 4 weeks after 48 h of nicotine administration by a transdermal patch [66, 67]. Correspondingly, retrospective case studies also found that application of a single transdermal nicotine patch delivering about 7 mg nicotine in 24 h resulted in a significant tic reduction for a mean of 10 days [239, 243]. The participants complained, however, about nausea and occasional headache and sedation. In the first randomized, double-blind study 70 patients with TS were treated with either transdermal nicotine (7 mg/24 h) or placebo patches in addition to their individual optimal dose of haloperidol [245]. In the patients who completed all 19 days of nicotine ($n = 27$) or placebo ($n = 29$), improvement of emotional and behavioral symptoms but also adverse reactions such as nausea and vomiting were more frequent under nicotine treatment. A subsequent randomized, double blind, placebo-controlled trial examined the acute (4 h) and sustained (2 weeks) effects of a single dose of transdermal nicotine on clinical (i.e., tics), attentional (continuous

performance task, event-related potential, patient and parental reports), and behavioral symptoms in 23 children and adolescents with TS receiving treatment with antipsychotic agents. In the 14 evaluable patients with complete primary efficacy data, nicotine (compared to placebo) failed to alter symptoms at 4 h but counteracted ERP-P300 signs of diminished attention seen 2 weeks following placebo treatment. Secondary efficacy measures, including patient self-reports and parental ratings, found nicotine to reduce complex tics and improve behaviors related to inattention [104]. One study investigated neurophysiological mechanisms possibly underlying nicotine treatment of TS by using transcranial magnetic stimulation (TMS). A single dose of nicotine in 10 non-smoking and non-treated adults with TS reduced tic severity as assessed by blind video scoring in the majority of patients. In addition, nicotine abolished the reduced inhibition in patients compared to controls [172].

Tetrahydrocannabinol (THC) has been suggested to be effective and safe in the treatment of tics [162–164] without influence on neuropsychological performance [161]. This knowledge is based on a randomized, double blind, placebo-controlled study in which 24 adult patients with TS were treated over a 6-week period with up to 10 mg THC/day. No serious adverse reaction occurred and the reported mild adverse reactions were dizziness, tiredness, and dry mouth. Hasan et al. [98] reported about a 15-year-old boy with treatment refractory TS plus ADHD leading to severe physical and psychosocial impairment. For the first time after several years of unsuccessful medication even with a combination of different agents, the administration of THC improved tics considerably without adverse reactions, allowing parallel stimulant treatment of coexisting ADHD. Along with the THC treatment, TMS measured cortical inhibition was increased.

In addition to the use of pharmacological treatment options with systemic effects, there is increasing evidence for the efficacy of *botulinum toxin injections* to treat persistent well-localized (non-complex) motor and, sometimes, vocal tics by temporarily weakening the associated muscles. Initially, botulinum toxin injection was used for selected severe cases [3, 107, 125, 229]. Other case reports and case series followed also including children after the age of 8 years [4, 131, 215, 257, 273, 279]. In 35 of 186 patients, botulinum toxin injections were effectively controlling motor tics [8]. The effect on vocal tics was minimal. Adverse reactions included temporary soreness and mild muscle weakness. In 30 patients with vocal tics assessment after 15 days and then 4 times over a 12-month period botulinum toxin injection improved vocal tics in 93% of patients, with 50% being tic-free [187]. Mean response time was 5.8 days and mean duration of response was 102 days. Quality of life improved and premonitory experiences dropped from 53 to 20%. Hypophonia was the only adverse reaction of note (80% of patients). Just recently, the positive short-term and long-term (up to 10 years) treatment effects of botulinum toxin injections every 3 months on simple motor tics of 15 patients (mean age 43 years; range 18–84) could be shown [190]. Marras et al. [144] concluded from their randomized, double blind, controlled clinical trial that the treated tic frequency as well as the urge associated with the treated tic were reduced by botulinum toxin injection. Still, the patients' subjective perception was that overall this treatment did not improve their condition. This is perhaps due to the fact that only selected subset of tics could be treated in each patient.

The dopamine autoagonist *talipexole* with putative preferential activity on presynaptic dopamine receptors was investigated one time in a randomized, double blind, placebo-controlled study [90]. In 13 adult men with TS, talipexole was poorly tolerated because of clinically significant sedation and dizziness. Tics did not improve at tolerable doses. These findings suggest that talipexole has no role in the regular management of tic disorders.

Clonazepam, a benzodiazepine which acts primarily on the GABAergic system, has a long history in the treatment of TS with dosages up to 6 mg/day [89]. Although there have been no placebo-controlled trials in TS, open-label studies have been carried out in adults [94, 274] and adolescents with TS [115, 264]. In a single-blind comparison with clonidine in 20 children, clonazepam was superior in suppressing tics [61]. In a single-blind clinical study of 20 patients with TS, those with high red blood cell-to-plasma choline ratios responded better to clonazepam than to haloperidol [152]. As with all benzodiazepines, tolerance and adverse reactions including sedation, short-term memory problems, ataxia, and paradoxic disinhibition often limit the use of clonazepam [89]. There are no data on other benzodiazepines except a case report about the therapeutic effect of low-dosage diazepam on facial tics in children [78].

The GABA B receptor agonist *baclofen*, which is used for the treatment of spasticity, has been examined in an open-label study in a large cohort of children with TS [8]. 250 of 264 patients on baclofen treatment experienced a significant decrease in the severity of tics. A small randomized, double blind, placebo-controlled study of baclofen in 10 children was inconclusive because there was a reduction in overall impairment but no changes in tic frequency or severity [251]. The results of these studies provide only modest support for the use of baclofen in TS. Common adverse reactions were sedation and drowsiness.

Other GABAergic drugs including the anticonvulsant *levetiracetam* have shown tic reduction in open studies on TS [9, 71]. Adverse reactions, however, as well as the finding that levetiracetam did not change the mean total

YGTSS and Clinical Global Impression score in a small randomized, double blind, crossover study ($n = 10$) [99] as well as in a randomized, double blind, placebo-controlled, crossover trial in 22 children with TS (mean age 12.2 years) [253] question its usefulness in the treatment of TS.

Topiramate reduced tics in a small randomized, double-blind study on 20 patients of a broad age range (7–65 years) compared to placebo [110]. This is in line with a chart review on 41 patients with TS [127] as well as a previous report on two patients with TS who were successfully treated with topiramate while previous medications were tapered and discontinued during the first 2 weeks of treatment [1].

Lithium has been used successfully to reduce tics in five of ten children and adolescents [121], a 22-year-old male [277], and three adolescents suffering from TS who had been initially treated with haloperidol [70]. Failure has also been described, though [26], and firmer evidence is lacking.

Several case reports [81, 220–222] and a randomized, double-blind, placebo-controlled study involving 10 adults with TS suggest that tic reduction may be achieved with *naloxone* [129], an opioid receptor antagonist. Some studies indicated that difference in response to naloxone in TS subjects may be based on a dose–response effect [38, 276].

Some attention has also been given to the use of treatments that include a modulation of the body's autoimmune-response. In children fulfilling criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS; a subgroup of children with OCD and/or tic disorder that experience symptom exacerbations following streptococcal infections), *plasma exchange* and *intravenous immunoglobulin* (*IVIG*) were both effective in lessening of symptoms [185, 293], although benefits through IVIG could not be confirmed in unselected patients with a tic disorder [101]. In a small prospective study, antibiotic prophylaxis with *penicillin* or *azithromycin* administered for 12 months in children fulfilling PANDAS criteria was associated with significant decreases in neuropsychiatric exacerbations [254]. A case study of a patient with TS reported benefits of treatment with *celecoxib*, a COX-2 inhibitor [165].

Finally, a *wide range of further neuroactive agents* have been examined non-systematically with divergent results concerning their efficacy in the treatment of TS. For example *buspirone* [65], *carbamazepine* [168, 292], *metoclopramide* [2, 169], *physostigmine* [258, 259], and *spiradoline mesylate* [39] have received some attention. A comprehensive overview of other case reports and non-blinded trials can be found elsewhere [195].

Treatment of tics in the context of comorbidities

Children and adolescents with TS are frequently affected by coexisting psychiatric conditions [79], which may be regarded the rule rather than the exception. In clinical samples of TS about half of the cases also meet criteria for ADHD and vice versa, TS is present in about 20% of children with ADHD [208, 228]. This co-occurrence of TS and ADHD is in most cases associated with a higher psychopathological, social, and academic impairment resulting from the negative impact of ADHD [10, 95, 200–202]. Besides, patients with TS also suffer more frequently from obsessive–compulsive symptoms or disorder (about 50%). Especially the need to achieve a ''just right'' feeling in TS has to be seen as an indicator for a continuum between TS and OCD [203].

Coexisting disorders cause often more clinical impairment and may be more responsive to treatment than the tics themselves [19]. It is therefore crucial to select an appropriate treatment goal (tics or coexisting conditions), when deciding on treatment options. Treatment of tics and coexisting conditions should be prioritized according to the impairment caused by each problem (for a decision tree see Fig. 1). Thus, in many cases not the tics, but coexisting problems require treatment e.g. ADHD or OCD. Clinicians should thus avoid to start two medications simultaneously, for instance one for tics and one for ADHD symptoms. Primary treatment of a coexisting condition, such as ADHD may reduce stress and improve attentional resources, and sometimes reduce tics by enhancing the individual's ability of tic suppression.

Treatment algorithms of coexisting conditions in the context of TS are similar to treatment of these conditions without the presence of TS. Well-designed controlled clinical trials have not indicated a deterioration of tics in persons treated with stimulants [21] nor induction of first tics by stimulant treatment even in children at risk [175, 204].

Long-term treatment with methylphenidate (MPH) is not associated with increases in tic severity. In a two year prospective, open label study in which effects of MPH treatment were evaluated in 34 prepubertal children with ADHD and with chronic multiple tic disorder, the authors found no evidence that motor or vocal tics changed in frequency or severity during the MPH maintenance therapy, whereas initial behavioral improvements were maintained [82]. In a subsequent blinded placebo-controlled discontinuation trial in 19 children with ADHD and with chronic tic disorder who had received psychostimulants for a minimum of one year, tics did not change in their frequency or severity of motor or vocal tics during the maintenance dose of stimulant medication compared with the placebo condition. Treatment with the maintenance dose was, however, associated with behavioral improvement in ADHD symptoms, indicating continued efficacy. These studies prove that neither

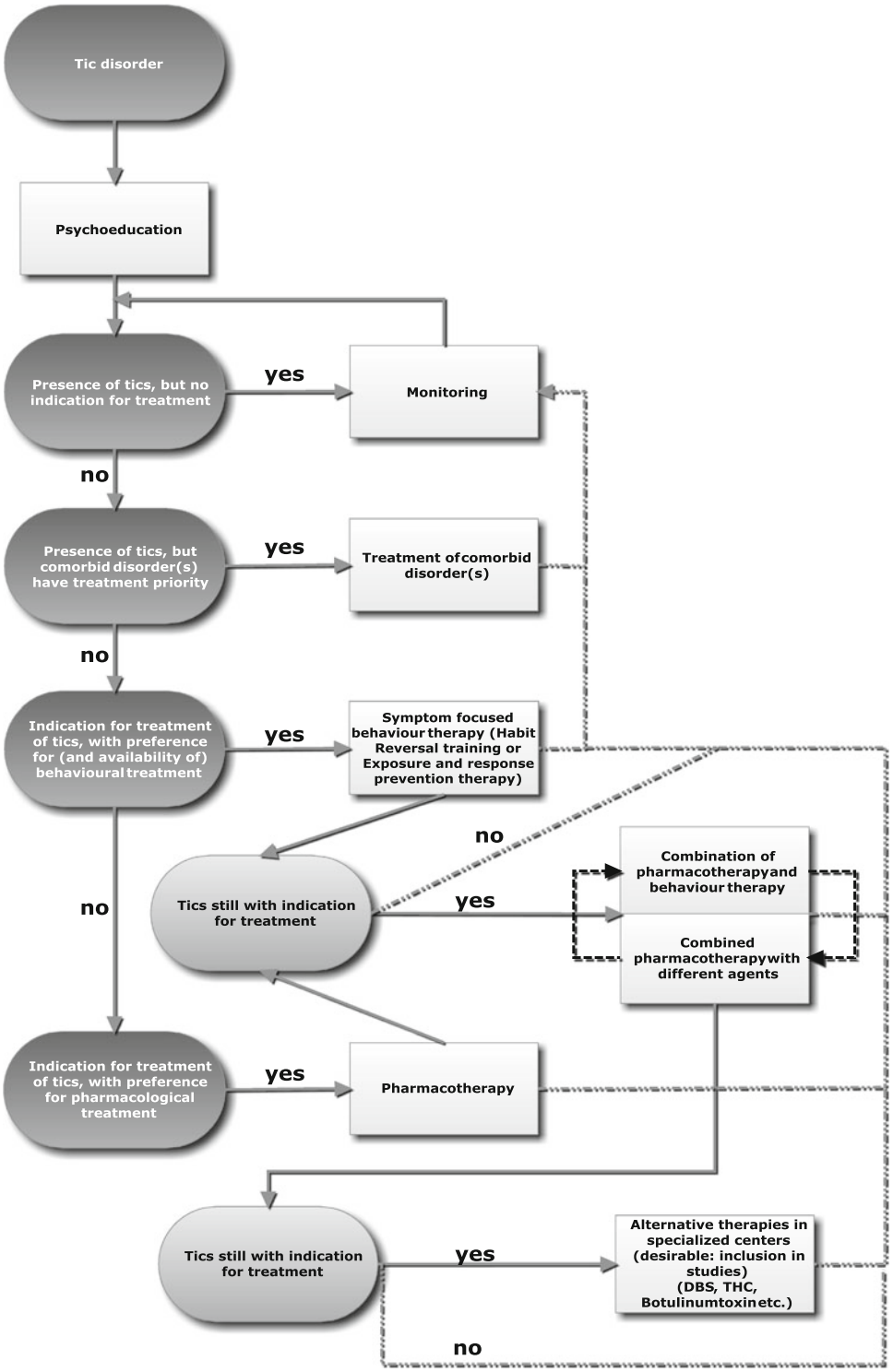

Fig. 1 Decision tree for the treatment of tic disorders including Tourette syndrome. Indications for treatment are given in "Tics cause subjective discomfort (e.g. pain or injury)", "Tics cause sustained social problems for the patient (e.g. social isolation or bullying)", "Tics cause social and emotional problems for the patient (e.g. reactive depressive symptoms)" and "Tics cause functional interference (e.g. impairment of academic achievements)". *Solid arrow* next level of evaluation/treatment, *dashed-dotted arrow* monitoring after successful treatment, *dashed arrow* alternating between two treatment options. Note: patient preference (after psychoeducation) and availability of therapists have to be considered in the choice of treatment. *DBS* deep brain stimulation, *THC* Tetrahydrocannabinol

treatment nor discontinuation of treatment with MPH in patients with tics lead to an exacerbation of tics. Thus, abrupt withdrawal of stimulant medication in children receiving long-term maintenance therapy does not appear to result in worsening of tic frequency or severity.

Higher doses of stimulants, in the range of 45 mg b.i.d. of MPH and 22.5 mg b.i.d. of dexamphetamine, however, may still lead to (reversible) tic exacerbations [36]. Thus, in general, stimulants may be safely used in children with TS and ADHD, when using doses based on the typical clinical titration procedure [21]. Other treatment options for ADHD in the context of TS include clonidine [271], atomoxetine [5, 256], and desipramine [255].

Coexisting OCD in patients with TS may be less responsive to serotonin reuptake inhibitor monotherapy compared to OCD in patients without tics [149]. Co-administration of an antipsychotic agent may be helpful [20, 56].

Problems with clinical recommendations for the pharmacological treatment of TS

Unfortunately, there has not been great improvement in evidence concerning the pharmacological treatment of TS since the overview of Robertson and Stern [199] who stated that "the treatment of the Gilles de la Tourette syndrome has evolved from case reports, clinical experience and more recently blinded trials usually in small numbers of patients". Ideally, according to the principles of evidence-based medicine to be recommended, an agent must have shown its efficacy in randomized, double-blind, placebo-controlled studies. However, even today, evidence for efficacy of many agents that might be considered in the pharmacological treatment of TS is often based on open studies or randomized, double-blind, placebo-controlled studies with quite small sample sizes [199]. Hence, there exists only one drug which has been approved for TS widely in Europe, which is haloperidol. However, because of its adverse reactions it is nowadays usually a drug of third line in clinical practice.

Particularly there is not a sufficient number of randomized, double-blind trials that have directly compared different pharmacological treatment options of TS including a placebo group [206, 214, 236]. Moreover, the heterogeneity of tic disorders with regard to the severity, frequency, localization, complexity of the tics as well as with regard to patterns of comorbidity demands further investigation in terms of the identification of factors that may predict or moderate response to different psychopharmacological agents [199]. Knowledge in this area could help clinicians to reach a more tailored choice of treatments. Currently, we have no data with regard to response to a second medication in patients who did not respond favorably to a first line agent. That is, for example, in patients who have not responded to risperidone, we do not have scientific data from trials whether response may be still expected from another antipsychotic, or rather from a different type of medication. Finally, durations of existing studies have not always taken into account the natural waxing and waning of tics (see Fig. 2). This calls for longer observation periods and better rating instruments than those of most existing studies. Investigations of long-term efficacy and adverse reactions are completely lacking. Nevertheless, the treating physician should be aware of the side effects profile of the drug in question and initiate adequate and suitable clinical and laboratory controls.

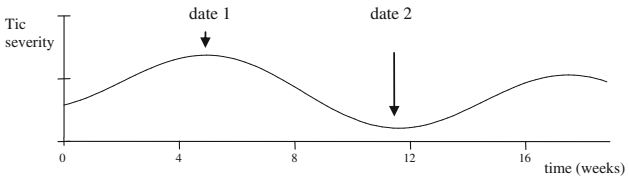

Fig. 2 Evaluation of treatment efficacy in TS in light of natural waxing and waning. At date 1 a therapeutic intervention could be followed by tic reduction despite of its potential to increase tics or without an effect on tics. This has to be ascribed not to causal mechanisms of the intervention but to the natural waxing and waning of the tics. Correspondingly, a therapeutic intervention at date 2 could be followed by an increase of TS symptomatology despite its potential to reduce tics. The therapeutic intervention might attenuate the natural waxing of the tics. Conclusion: Meaningful appraisal of treatment efficacy in TS can only be given in most cases after longer time

Moreover, studies comparing the effectiveness of behavioral and pharmacological treatments in patients with TS are absent. Thus, currently no scientific data are available indicating whether behavioral treatment or medication should generally be tried first. An advantage of behavioral treatments may be its better long term effects, beyond the duration of the therapy, as well as their assumed less frequent and less severe adverse reactions. However, behavioral treatments require sufficient motivation and certain ability for introspection, which may limit its usefulness somewhat in younger patients (see also Verdellen et al., this issue). Patients' treatment preference after thorough psychoeducation is an important aspect in deciding between medication and behavioral therapy. Definitely, pharmacologic treatment should be initiated if behavioral treatment reveals insufficient success. Conversely, drug-treated patients who do not experience sufficient tic reduction and/or suffer from non-tolerable adverse reactions may be stimulated to (re-)start behavioral interventions. In the rare cases of adults, who have extremely impairing tics that are not sufficiently alleviated through several pharmacological treatment options one

should consider deep brain stimulation (see Mueller-Vahl et al., this issue).

Assessing response to treatment

The clinician should inform the patient and their parents that the goal of a pharmacological treatment of TS is not to completely eliminate the tics, but to achieve a reduction aimed at eliminating the psychosocial impairment caused by the tics. Unrealistic expectations on the efficacy of pharmacological treatment of TS will lead to frustration for the child, family, and physician. Also, the desire to completely suppress tics can lead to overmedication and adverse reactions that cause more problems than the tics themselves. A common example of this is the overtreating of children to the point of excessive daytime sedation or unhealthy weight gain. Families should be informed that medication typically only results in a 25 to 50% reduction in tic symptoms.

Also, clinicians should always be aware of the natural waxing and waning of tics in TS when evaluating effects of treatments (see Fig. 2). It is advisable to consistently use formal tic severity rating scales to more objectively assess responses to treatment over time. Perhaps the most suitable instrument is the YGTSS, a semi-structured interview which records the number, frequency, intensity, complexity, and interference of motor and vocal tics separately [135]. But also the Tourette Syndrome Severity Scale (TSSS) developed by Shapiro et al. [235], which is shorter and more easy to use can be recommended.

What specific agents can be recommended?

As previously stated, there is a great scarcity of studies directly comparing efficacy and safety of different psychopharmacological agents, foremost with regard to longer term effects. Therefore every general recommendation depends heavily on the experts' own experiences and preferences.

After reviewing the existing literature, it appears that the best evidence arising from randomized, double-blind, placebo-controlled studies is still available for the typical antipsychotics haloperidol and pimozide, with some indications that pimozide may be more effective and may have a somewhat more favorable adverse reaction profile than haloperidol [189], with exception of its potential cardiac effect. In clinical practice in Europe, however, over the last years haloperidol and pimozide have been replaced stepwise by atypical antipsychotics. Here, the best evidence is undoubtedly available for risperidone [186, 189]. This is also the agent that has been studied best. A lower risk for adverse reactions compared to typical psychotics is assumed in clinical use. Still many adverse reactions, however, are similar to those associated with the use of typical antipsychotics, including sedation, akathisia, weight gain, extrapyramidal symptoms (EPS), neuromalignant syndrome, and tardive dyskinesia. Although atypical antipsychotics generally are associated with a lower incidence of EPS in youth [269], a rapid dose escalation is actually associated with higher risk of EPS [37]. In addition, longer experience with atypical antipsychotics reveals that new risks need to be considered, such as metabolic syndromes and QTc prolongation. The incidence of these risks in patients suffering from TS, especially in children and adolescents, cannot be easily predicted due to the paucity of long-term studies in this population.

The choice of pharmacological treatments is not only based on the efficacy and the rate of adverse reactions but also on the potential to show efficacy in refractory cases. In particular, aripiprazole is rather promising, given the lower probability of weight gain as adverse reaction and promising effects in patients who had not responded to previous treatments. Placebo-controlled studies with aripripazole are still missing, however.

Availability of clinical experience with agents also plays an important role in the choice of recommendable treatments. In the German-speaking world the benzamides, such as tiapride and sulpiride are commonly used as first line agents to treat TS particularly in children and adolescents. Indeed, tiapride is regarded as the medication of first choice in the German guidelines for the treatment of tic disorders without coexisting significant emotional/obsessive–compulsive symptoms [207], Tiapride and sulpiride are not available in the United States. This explains why these agents are not mentioned in reviews from US authors [87] and why their clinical efficacy in TS as well as their pharmacological properties have been underinvestigated in comparison to other antipsychotic compounds. This small base of evidence notwithstanding, Robertson and Stern [199] conclude in their review that tiapride and sulpiride are highly recommendable to treat TS in view of their excellent balance of efficacy and tolerability proven over decades in clinical practice.

Further, severity of tics and presence of comorbidity may affect choices of treatments. Although the evidence in favor of the tic-suppressing effects of clonidine may be less robust compared to the antipsychotics, clonidine may actually improve ADHD symptoms alongside with suppression of especially mild-to-moderate tics. In addition, clonidine tends to alleviate initial insomnia and reduce anxiety [217].

An important consideration, given the relative lack of controlled clinical studies, is the opinion of experts. Therefore, we sent by email a questionnaire to members of the European Society for the Study of TS (ESSTS). All clinicians with ample experience in the treatment of TS

Table 1 Most common and important medication for pharmacologic treatment of Tourette syndrome and other chronic tic disorders

Medication	Indication	Start dosage (mg)	Therapeutic range (mg)	Frequent adverse reactions	Physical examinations– at start and at control	Level of evidence
Alpha-adrenergic Agonists						
Clonidine	ADHD/TS	0.05	0.1–0.3	Orthostatic hypotension, sedation, sleepiness	Bloodpressure, ECG	A
Guanfacin	ADHD/TS	0.5–1.0	1.0–4.0	Orthostatic hypotension, sedation, sleepiness	Bloodpressure, ECG	A
Typical Neuroleptics						
Haloperidol	TS	0.25–0.5	0.25–15.0	EPS, sedation, increased appeitite	Bloodcount, ECG, weight, transaminases, neurologic status, prolactine	A
Pimozide	TS	0.5–1.0	1.0–6.0	EPS, sedation, increased appeitite	Bloodcount, ECG, weight, transaminases, neurologic status, prolactine	A
Atypical Neuroleptics						
Aripirazole	TS	2.50	2.5–30	Sedation, akathisia, EPS, headache, increased appetite (less than other neuroleptics), orthostatic hypotension	Bloodcount, bloodpressure, weight, ECG, transaminases, bloodsugar	C
Olanzapine	TS/OCB	2.5–5.0	2.5–20.0	Sedation, increased appeitite, akathisia	Bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	B
Quetapine	TS	100–150	100–600	Sedation, increased appeitite, agitation, orthostatic hypotension	Bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	C
Risperidone	TS/DBD	0.25	0.25–6.0	EPS, sedation, increased appeitite,orthostatic hypotension	Bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	A
Ziprasidone	TS	5.0–10.0	5.0–10.0	EPS, sedation	Bloodcount, ECG, weight, transaminases, prolactine	A
Benzamides						
Sulpiride	TS/OCB	50–100 (2 mg/kg)	2–10 mg/kg	Problems with sleep, agitation, increased appetite	Bloodcount, ECG, weight, transaminases, prolactine, electrolytes	B
Tiapride	TS	50–100 (2 mg/kg)	2–10 mg/kg	Sedation, increased appetite	Bloodcount, ECG, weight, transaminases, prolactine, electrolytes	B

Evidence level: A (>2 controlled randomized trials), B (1 controlled, randomized trial), C (case studies, open trials)

DBD disruptive behavior disorder, *OCB* obsessive–compulsive behavior, *TS* Tourette syndrome, *EPS* extrapyramidal symptoms

Table 2 European experts' recommendation for the treatment of tics for children and adolescents, based on response to the question, which medication the expert clinician would consider first, second, third, and subsequent choices in, provided there would be no contra-indication for any of the available agents and no comorbidity

Agent	Expert rating
Risperidone	60
Clonidine	37
Aripiprazole	33
Pimozide	32
Sulpiride	24
Tiapride	21
Haloperidol	17
Tetrabenazine	9
Ziprasidone	6
Quetiapine	4
Tetrahydrocannabinol	2
Desipramine	1
Botulinum toxin	1
Thioridazine	1
Guanfacine	1
Oxcarbazepine	1
Atomoxetine	1

We received 22 responses out of 60 questionnaires and rated each first choice agent with 4 points, a second choice agent with 3 points, a third-choice agent with 2 points, and additional agents with 1 point

were asked what psychopharmacological agent they would consider first, second, third, and subsequent choices in the treatment of tics (provided there would be no contra-indication for any of the available agents, and there would be no comorbidity). We received 22 responses out of the 60 members. We rated each first choice agent with 4 points, a second choice agent with 3 points, a third-choice agent with 2 points, and additional agents with 1 point. As listed in Table 1, most support from the experts has been provided for risperidone, with considerable support for clonidine, aripiprazole, and pimozide as well (Table 2).

Based on the available evidence, experience with the drug, and experts' preference, risperidone can be recommended as a first choice agent for the treatment of tics. Adverse reactions form the biggest limitation of risperidone, foremost so weight gain and sedation. Other drugs merit recommendation as well. Relatively good evidence with a better adverse reaction profile than haloperidol is available for pimozide. Tiapride and sulpiride can be recommended based on the broad clinical experience and favorable adverse reaction profile, although more controlled clinical studies are required. Aripipazole has great potential especially in treatment refractory cases and probably less pronounced risk of severe weight gain. Finally, clonidine can be given especially when coexisting ADHD is present. All other agents mentioned in Table 1 may be considered as alternatives, once response to one or more of the earlier mentioned medications has been unsatisfactory.

In case of coexisting OCD, risperidone forms a good first choice also, based on the results of clinical trials. This may be combined with a serotonin reuptake inhibitor. Given the continuum of tics and obsessive–compulsive symptoms, other agents recommended for the treatment of tics may be tried as well; when partial response occurs, addition of a serotonin reuptake inhibitor or of behavioral treatment may be considered. Coexisting ADHD may be treated with stimulants, atomoxetine, or clonidine. This may be combined with an (antipsychotic) agent for the tics.

The current guidelines do not contain dosage recommendations of each agent. In general, dosage should start low and gradually increase with close monitoring of response and adverse reactions. Most published studies have included both children and adults, up to date, no evidence suggests that the two age-groups should be treated in different ways apart from drug dosages [73, 199]. There are several hints that dosage of pharmacotherapy of TS is not different between children, adolescents, and adults once body weight has been taken into account [213, 282], but clear data are lacking. A commonly unrecognized problem is the miss of adapting the dosage to the increasing body weight during maturation.

To the best of our knowledge, only one drug is formally licensed for the indication tics or TS in most European countries: haloperidol. With all other medications (actual exceptions of a certain country cannot be excluded), prescription is on an off-label base, reflecting the paucity of efficacy and safety data, which would not be sufficient for approval by a registration authority for any of the mentioned agents. This should always be discussed with families prior to initiation of treatment.

The proposed principles of practice are considered as guidelines only. We hope that this guideline may contribute to an improvement in the pharmacological management of patients with tic disorders. The individual treatment of a patient should be planned by considering the available diagnostic information, the level of impairment associated with tics, the efficacy data and adverse reactions of treatment options as well as patient's preference to gain the best result and adherence possible.

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