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REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders: summary statement

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Abstract

In 2011 a working group of the European Society for the Study of Tourette syndrome (ESSTS) developed the first European Guidelines for Tourette syndrome (TS) published in the ECAP journal. After a decade ESSTS now presents updated guidelines, divided into four sections: Part I: assessment, Part II: psychological interventions, Part III: pharmacological treatment and Part IV: deep brain stimulation (DBS). In this paper, we summarise new developments described in the guidelines with respect to assessment and treatment of tics. Further, summary findings from a recent survey conducted amongst TS experts on these same topics are presented, as well as the first European patient representative statement on research. Finally, an updated decision tree is introduced providing a practical algorithm for the treatment of patients with TS. Interestingly, in the last decade there has been a significant shift in assessment and treatment of tics, with more emphasis on non-pharmacological treatments.

Keywords Tourette syndrome · Tics · Comorbidities · Guidelines · Treatment · Classification

Tourette syndrome (TS)[1] is a neurodevelopmental disorder at the crossroads between neurology, neuropaediatrics, and psychiatry. This is reflected for instance in the notion that tics, the hallmark of TS, are the result of involuntary motor disinhibition on the one hand, but are on the other hand, at least in part, under volitional control and can be voluntarily suppressed.

In 2011 ESSTS working groups have published the first "European Clinical Guidelines for Tourette syndrome and Other Tic Disorders" in the ECAP journal. Structured in four parts, these guidelines summarised the best available

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[1] We use the term TS in these guidelines, wherever information also applies to other forms of tic disorders. Only if there are substantial, well-known differences between TS and other forms of tic disorders, we use TS or other terms, e.g. transient or chronic motor tic disorder.

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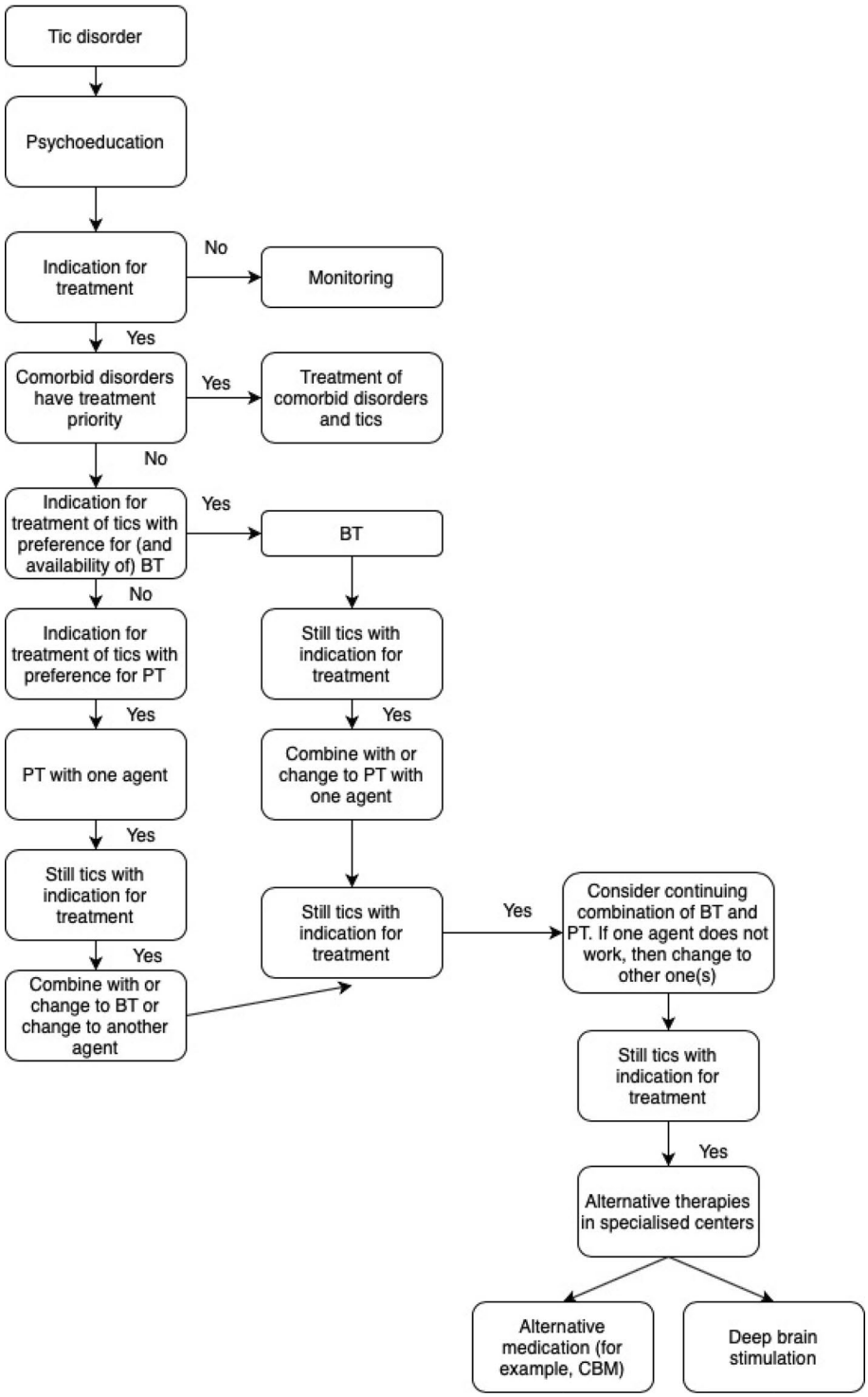

Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine

evidence combined with best practice expert consensus on the assessment and treatment of TS and related conditions: Part I: assessment [3], Part II: psychological interventions [17], Part III: pharmacological treatment [14], and Part IV: deep brain stimulation (DBS) [9]. The ESSTS guidelines have since then been used throughout Europe and have been cited over 500 times.

In the current special section of ECAP, we present an update of the four parts of the ESSTS guidelines published in 2011, supplemented with a decision tree providing a practical algorithm for the treatment of patients with TS (see Fig. 1) and a patient representative statement on research priorities. All parts together provide a comprehensive guideline that covers assessment and all forms of treatments.

Since both empirical research findings and clinical knowledge are important elements of clinical guidelines, these guidelines therefore entail not only a thorough review of the evidence-based literature, but also the results of a survey conducted among ESSTS experts on the assessment and treatment of TS, which are incorporated in each part of the current guidelines.

Recently the American Academy of Neurology (AAN) has published a systematic review [12] as well as practice guideline recommendations [13]—in which several ESSTS experts participated—on the effectiveness and safety of treatments for tics. Nonetheless, in our opinion, the present updated European clinical guidelines have a *raison d'être.* Through surveying ESSTS experts on assessment and treatment in both clinical practice and research, we were able to specifically incorporate knowledge and expertise from a large number of European experts into the guidelines. Further, despite overlap between Europe and the US/Canada, there are notable differences with respect to assessment and interventions in clinical practice. This is reflected by differences in health care use and organisation, in patient preferences and in first choice of pharmacological agents, availability and application of behavioural treatments, costs of treatment, and approval status. In the following paragraphs we summarise the most important conclusions formulated in each part of the guidelines.

In Part I: assessment, we have incorporated the newly implemented DSM-5 and ICD-11 criteria. We summarise available literature that includes newly developed tic rating scales and give concrete recommendations for assessments of tics and psychiatric comorbidities in the context of both routine practice and research. In addition, we advice how to differentiate tics and functional "tic-like" movements and "Tourette-like" behaviours [11]. In the DSM-5, the position of tic disorders has remained largely the same as in DSM-IV-TR, classifying TS as a "neurodevelopmental disorder", alongside attention deficit/hyperactivity disorder (ADHD), intellectual disabilities and autism spectrum disorder (ASD). In the ICD-11, in contrast, tic disorders have been removed out of the ICD-10 category "Behavioural and emotional disorders with onset usually occurring in childhood and adolescence" and reassigned to the movement disorders section. In our opinion, this disregards the growing body of both genetic and clinical evidence that tic disorders are related to developmental and psychiatric disorders rather than to neurological disorders [2, 4]. Furthermore, in our opinion, there is no scientific evidence to support introduction of a subcategory "Infectious or post-infectious tics" (8A05.10) in the category "8A05.1 Secondary tics" [8]. Therefore, we do not recommend assessment of children for Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)-related TS. Moreover, introduction in ICD-11 of the secondary tics subcategory named "Tics associated with developmental disorders" (8A05.1.1) leaves room for confusion; when a person meets criteria for both tics and ASD or ADHD, he/she can be classified as suffering from either "Tics associated with developmental disorders" (8A05.11), or from TS in combination with ASD. In our opinion, current evidence indicates that tic disorders *are* by definition neurodevelopmental disorders.

With respect to behavioural interventions, in part II: psychological interventions, we outline substantial progress that has been made since 2011. Most importantly, since then several randomised controlled trials (RCTs) have been published on habit reversal treatment in both children and adults. As a result, behavioural treatment is currently regarded as the treatment of choice in reducing tics. Accordingly, with this up-date guidelines we changed the order of part II and part III. Further, internet-based modules of established behavioural treatments have been developed to render behaviour therapy more accessible. In addition, adaptations have been made to broaden the focus of behavioural treatment from reducing tic severity only to improving the individual's overall quality of life.

With respect to pharmacological treatment (part III), most importantly, the antipsychotic agent aripiprazole has been proven effective in the treatment of tics in large-scale RCT [15, 19] and is currently the most frequently prescribed drug in Europe according to the ESSTS survey. During the last decade, three important trends can be noted. First, in contrast to the situation pre-2011, almost all RCTs have been sponsored by pharmaceutical companies which clearly increased the database but also bears the risk of bias [6]. Second, according to the AAN guidelines the traditional Chinese medicine products 5-ling granule and Ningdong granule have now made it to the list of compounds showing moderate confidence in evidence of treatment effects. However, we are not in accordance with this confidence for the following reasons: (i) Investigational Medicinal Product Dossier (IMPD) information that includes safety information of these agents is extremely limited; and (ii) agents contain products such as dried human placenta and therefore are not allowed on the European market. During recent years, several large scale RCTs have been conducted in China [14]. Although they may contain potentially important information, they have been almost exclusively published in Chinese [18]. Therefore, it is impossible to judge upon the quality of these trials for readers not mastering Chinese.

Although some new pharmacological compounds are currently under investigation to treat tics, first results were disappointing: both the vesicular monoamine transport (VMAT) inhibitor deutetrabenazine [16] as well as the inhibitor of the monoacylglycerol lipase (MAGL) and selective modulator of the endocannabinoid system Lu AG06466 (former ABX-1431) [10] did not meet the primary endpoint of tic reduction in phase 2/3 studies. Therefore, results from

RCTs investigating efficacy and safety of ecopipam, a selective antagonist of dopamine D1-type receptors (ClinicalTrials.gov Identifier: NCT01244633), but also nabiximols, a cannabis extract containing tetrahydrocannabinol (THC) and cannabidiol (CBD) at a 1:1 ratio (ClinicalTrials.gov Identifier: NCT03087201), are highly anticipated.

With respect to deep brain stimulation (DBS), in part IV, we present increasing knowledge about efficacy in TS, although numbers and sample sizes of RCTs are still very limited. Reported effects are modest and partly even contradictory with effect sizes of tic improvement between 0.36 and 1.56. European contributions to a meta-analysis [1] and data of the International Tourette syndrome DBS Public Database and Registry [7] have contributed significantly to interpret the heterogeneous results [1, 7].

In order to incorporate clinical knowledge that reflects actual clinical practice in Europe into our revised and updated ESSTS guidelines, between October and November 2019 we conducted an online survey among ESSTS members. This was a follow-up to a prior survey carried out in the context of the 2011 guidelines, which allowed to capture the changes in assessment and treatment practices over the last decade [14]. We received responses from 59 experts from 17 different European countries predominantly from specialised outpatient clinics seeing on average 72 (range 0–600) children, 64 (range 0–666) adolescents, and 40 (range 0–300) adults with tics per year. Of note, experts encompassed child and adolescent psychiatrists ($n=20$, 34%), psychologists ($n=11$, 19%), adult neurologists ($n=13$, 22%), and adult psychiatrists ($n=11$, 19%) (several answers missing). Remarkably, 53% ($n=31$) of experts conduct both clinical and research work, while 34% ($n=20$) work only clinically and 10% ($n=6$) are exclusively dedicated to research (several answers missing).

While detailed results of the survey have been added to the four different parts of the updated guidelines, here we briefly highlight the most relevant findings: (i) there is large agreement amongst European TS experts that in clinical practice tic severity assessment is based on clinical judgement complemented with observational and interview data including the Yale Global Tic Severity Scale (YGTSS) [5], the latter being the most widely used rating scale for tic assessment both in clinical practice and research; (ii) for the majority of ESSTS experts shared decision-making is common practice in the treatment of patients with TS, aiming to help patients to reach evidence-informed and value-congruent medical decisions; (iii) behavioural therapy was reported to be the first line treatment in both children and adults with tics, but was available in only 57% of centres. In contrast, 65% of experts consider pharmacotherapy when requested; (iv) all over Europe, there is still a substantial lack of trained psychotherapists so that only about half of the patients recommended for behavioural therapy can receive it; (v) as a consequence, internet (known as telemedicine or telehealth) as well as group-based treatment strategies are being introduced in clinical routine practice. Fortunately, different RCTs are currently ongoing investigating the efficacy of different kinds of internet-delivered behavioural therapy; (vi) the majority of experts recommends pharmacotherapy when behavioural therapy has been unsuccessful (72%) or in combination with behavioural therapy for severely affected patients (89%); (vii) compared to 2011, ESSTS experts have shifted from risperidone to mostly using aripiprazole as a first-line therapy followed by risperidone, clonidine, guanfacine (children) and topiramate (adults), respectively; (viii) remarkably, haloperidol, although being the only officially licenced drug for tic treatment in most European countries, is no longer used as a preferred drug by European experts (used by 6 (10%) experts in children/adolescents and 7 (12%) in adults, respectively); (ix) ESSTS experts consider DBS only in carefully selected and otherwise treatment-refractory patients corresponding to fewer than 3% of all patients. Although introduced already in 1999, DBS is still offered in only about 25% of highly specialised TS clinics.

Finally and uniquely, a paper by patients representatives in Europe who conducted a world-wide survey among patient advocacy groups, describes the patient perspective on different research topics. Unsurprisingly, three quarters of the 2000 respondents indicated that they would prefer research into the topic "how to treat TS and/or decrease symptoms".

In conclusion, our revised ESSTS guidelines contain updated information on recent developments on assessment and treatment of TS, combined with a patient representative statement, which expresses the close and fruitful collaboration between advocacy groups and experts in the ESSTS community.

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Declaration

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EDITORIAL

Updated European guidelines for Tourette syndrome: and now use them!

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This focused issue of *European Child and Adolescent Psychiatry* contains fully updated guidelines for the assessment and treatment of Tourette syndrome, written by European experts. The articles provide very useful practical recommendations for optimal care of children and adolescents with a tic disorder, spanning assessment, [1] psychological interventions [2], pharmacological treatments [3], and deep brain stimulation [4]. Recommendations are not only based on evidence from clinical trials but also took clinical experience into account to fill the existing gaps of evidence. Uniquely, also a report on patients' perspectives on research and treatment is included, indicating the need for more research into better treatments and problems in the day-to-day lives of patients with Tourette syndrome [5].

European Child and Adolescent Psychiatry very much encourages other European expert groups to submit guideline papers for disorders in our field. Guidelines are an important prerequisite for delivering the best care to our patients. Empirical evidence has repeatedly shown that assessment and treatment in accordance with expert guidelines greatly benefits the outcome of clinical care [6]. A classic example is the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (ADHD), [7] which showed that carefully crafted medication management according to guidelines is vastly superior to routine community care (even if that includes medication) as typically delivered in clinical practice.

Unfortunately, however, it is not the lack of clinical guidelines or existing gaps in the base of evidence underlying some recommendations, but rather the limited adherence to available guidelines that forms the weakest link in delivering evidence-based care in clinical practice in the field of pediatric mental health care. A number of recently published studies have indeed highlighted subpar adherence to available guidelines. A study among mental health clinicians across Europe found that 46% of them were unaware of the existence of guidelines in their country for the treatment of severe behavioral problems in children, and of the ones who were aware, 37.6% did not use them in practice [8]. More than 40% of Dutch clinicians reported using ADHD guidelines only 'sometimes', or less [9]. Many clinicians indicated to deviate from these guidelines in their daily practice, which is most concerning with regard to parent training: as many as one-third of the clinicians only advised the use of parent training in a minority of the children with ADHD in their practice, whereas guidelines uniformly recommend parent training as preferred first-choice treatment for all children with ADHD. This practice clearly bears the risk of starting ADHD medication where this is not (yet) indicated.

A study from Germany that assessed patient records of 73 clinicians regarding their handling of ADHD in their daily practice found only moderate adherence to most mandatory guideline components [10]. Particularly disappointing were insufficient involvement of teachers and schools in the treatment process, limited implementation of psychoeducational methods, as well as a lack of careful examination of patients, including monitoring of treatment effects during titration trials. Insufficient ongoing monitoring of children on ADHD medication, particularly with regard to documenting heart rate, blood pressure, and weight were also found in an investigation of medical records of children with ADHD from Australia against indicators derived from guideline recommendations [11]. That study also reported that the intended treatment duration with ADHD medication and signals for stopping the medication were often not documented prior to prescription.

Strikingly, a documented ADHD diagnosis was absent in about one in 10 patients who were prescribed ADHD

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medication according to the results of an analysis of German claims data, including 18,703 children and adolescents aged with a first-time dispensation of ADHD medication in the period 2015–2017 [12]. This contrasts with German guideline recommendations that require a structured, comprehensive ADHD assessment prior to prescribing ADHD medication. Another finding of that study was that 2.6% of all first-time prescriptions concerned second-line ADHD medication (e.g., lisdexamfetamine, guanfacine, dexamfetamine). This is clearly not constituting rational pharmacotherapy, given the less favorable efficacy and safety picture of second-line ADHD medication compared to first-line options. Australian general practitioners were deviating from recommendations to use stimulants ahead of other ADHD medications in almost a quarter of cases [11].

Adherence to guidelines regarding other classes of psychotropic medication has also been found to be disappointing. In an assessment of medical records from the Netherlands for adherence to guideline recommendations for antipsychotic prescription off-label prescribed for behavioral problems in children and adolescents, we found that the recommended screening of contra-indications prior to prescription was very rarely adhered to (below 20% of cases) [13]. Moreover, the important guideline recommendation that antipsychotics for behavior problems should only be prescribed in combination with psychosocial interventions was met in a mere 37% of the reviewed medical records. Simultaneous use of multiple antipsychotics occurred in as many as 3.2% of cases, a clear violation of guidelines. Younger children were found to be most at risk of receiving suboptimal care, warranting special attention to this vulnerable group.

Clinical practice regarding the use of antidepressants in young people is also worrisome. Guidelines for the treatment of depression recommend to start with fluoxetine, as the evidence for its efficacy is strongest and the risk of suicidality lowest, and also recommend to use a low starting dose. However, an investigation of data from a Dutch pharmacy prescription database indicated that it was not fluoxetine, but paroxetine and citalopram that were the most commonly prescribed first-use antidepressants in minors [14]. Moreover, starting doses were guideline concordant in only 58% of the time for children, 31% for preteens, and 16% for teens. A Danish study found that less than a quarter of the parents were informed specifically about suicidality as possible adverse events of antidepressants [15].

How can better use of guideline commendations be reached? The studies that we reviewed offer some clear clues. Foremost, awareness of the very existence of guidelines should be increased [8]. For this to happen, guideline training should be an essential component of (continuing) education programs for both medical and non-medical professions. Another useful way to increase guideline use is to improve the ease of applicability of these guidelines, for example, by developing an app with guideline-based decision trees or guideline checks embedded in electronic patient records [9]. Especially rational pharmacotherapy could be enhanced by incorporating a more standardized and mandatory documentation of the essential treatment steps in the medical record [13]. Other interventions to increase adherence to guidelines include provision of educational materials, performance of regular practice audits with feedback to individual clinicians, and raising awareness and limiting the role of marketing activities by pharmaceutical companies [14].

Adherence to guidelines is more likely when recommendations are specific and concrete and when few additional resources are required for implementation [14]. We do believe that the updated European guidelines for the assessment and treatment of Tourette syndrome meet these requirements. They have been written with practical applicability in mind. Included is a very useful clinical decision tree for the treatment of patients with Tourette syndrome based on shared clinician-patient decision making, outlining the various treatment steps that may be applied [16]. Obviously, we very much encourage applying our recommendations in clinical practice. Applicability for busy clinicians could be increased by making summary cards in the various European languages, which may also be used in continuous education programs. It is recommended to make such information available online, as part of websites that summarize recommended assessment and treatment steps for pediatric mental disorders. To enhance shared patient-clinician decision making, it will also be important to make psychoeducational information leaflets with recommended steps for assessment and treatment directed at children, their families, and schools, in co-operation with patient associations and to make sure these are also available online in all European countries.

At last, we are curious if the pandemic (i.e., not corona associated) phenomenon of "functional tics" [17] will ebb again or will be an elementary part of the next update of the European guidelines.

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REVIEW

European clinical guidelines for Tourette Syndrome and other tic disorders: patients' perspectives on research and treatment

Seonaid Morag Anderson[1] on behalf of on behalf of Tics and Tourette Around the Globe (TTAG) representing Tic and Tourette Syndrome (TS) patient associations around the world[1]

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Abstract
The formation of a new umbrella organisation called Tics and Tourette Across the Globe (TTAG) representing Tic and Tourette Syndrome (TS) patient associations around the world has led to a clearer voice for patients with Tourette Syndrome (TS). An opportunity has been created for this group to bridge research, clinical work and shared decision-making between researchers, clinicians and patients across Europe, with the result of improving the treatment and management of TS. A survey was sent out to capture the patients' perspective on research and treatment, and 2269 participants responded. 71% of participants reported they would prefer research into how to treat TS and/or make symptoms better. The inclusion of patients' perspectives on research and treatment in the updated European clinical guidelines for TS and other tic disorders highlights the new opportunities that have been created for the participation of patients in the discussion of TS research.

Keywords Tics · Tourette Syndrome · Patients · Guidelines · European Society for the Study of Tourette Syndrome (ESSTS) · Tics and Tourette Around the Globe (TTAG) · Patient and Public Involvement (PPI) · Research

Introduction

The new association TTAG are delighted that the European clinical guidelines for Tourette Syndrome (TS) and other tic disorders have been updated in 2021 and greatly welcome this opportunity to provide patients' perspectives on research and treatment.

Traditionally, patients have been involved in research as research participants in randomized controlled studies, or as respondents to questionnaires and interviews, or as fundraisers for research [1]. Previously Patient and Public Involvement (PPI) may have been misunderstood by researchers to be raising awareness of research, sharing knowledge or recruiting patients as participants. Initiatives to improve PPI have more recently led to 'more about engaging the members of the public and creating a dialogue with them to drive research forward and make it more patient centred'[2]. Nowadays medical and health research is more inclined to actively involve patients in the designing of research itself [3, 5]. The changing landscape of recent research agendas is influenced by many factors but one of them in recent years must be the 'overwhelming patient/public "push" to be involved in research governance, and that integrating PPI in trial design increases recruitment success' [4].

International patient support associations for different health conditions have advocated patients' involvement in research as partners [1, 6]. This means that patients worldwide have voiced a desire to be actively involved in designing medical research in many health conditions including TS. Patients have the aspiration to be involved in every stage of the research cycle including setting the research agendas [1, 3].

There is also the added value of a broader patient participation in research which has the potential to result in better and more accurate research outcomes as well as bringing the patients' perspective into research. One of the added benefits is that it maximizes partnership between stakeholders such as the researchers and patients recognised in the increasingly requested requirement from research ethics committees to include PPI in ethics applications. However, it has been noted that 'PPI is not yet firmly embedded or adequately formalised in European healthcare systems and research, possibly due to a lack of infrastructure, guidance and support' [7].

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More patient participation in research would also be to the benefit of scientists and clinicians as their research would have a better chance to meet the wishes, needs and treatment adherence of patients. People living with certain health conditions and their families have an inherent understanding of the needs they face and their input on research priorities has the potential to enrich the research questions being asked. Initiatives such as Priority Setting Partnerships by The James Lind Alliance with patients, clinicians and carers would seem to be a step in the right direction but as yet has not been done for people with Tourette Syndrome.

There is a whole terminology in how patients can be involved in research—knowledge sharing, authentic involvement, patient partner (PP) perspective, patient-oriented research (POR) and shared dialogue with co-production being shown as the gold standard. The most important factors in the success of PPI include 'the relationship between researcher and contributors, and particularly researcher willingness to change their approach in response to feedback' [8]. Patient involvement in research agenda setting is suggested to depend on 'the quality of attitude and engagement of researchers and funding agencies' [9].

Since 2010 TS patient association representatives have met at the annual conference of ESSTS (European Society for the Study of Tourette Syndrome). Often there up around nineteen countries involved with TTAG an average of 10 countries attending ESSTS annually. In general, there is a move towards a more patient-centered view in clinical care and the TTAG organisation has been working towards more active patient participation in the research process via various initiatives. A principle the TTAG organisation considers as core is bridging research and clinical work, and the understanding of shared decision-making in treatment between researchers, clinicians and patients, as part of evidence-based medicine [10]. We would like to extend this notion to research issues.

Methodology

To investigate patients' perspective on research and treatment, a research survey for Tourette Syndrome was conducted in 2018 with patients with TS and their parents, partners or other family members. This was the first time patients and their families with TS across Europe had been asked about their perspective on research and treatment options. The participants were asked what they would prefer to see research on, being asked to choose between causes or treatments. They were requested to prioritise what kind of research they would like to see into Tourette Syndrome and given options. Finally, they were asked about their knowledge of different kinds of treatment and whether they had been offered it in their own country.

The survey was anonymous and made available in 13 languages (Czech, Danish, Dutch, English, Finnish, French, German, Greek, Hungarian, Italian, Norwegian, Polish and Spanish). The survey link was sent to all known patient representatives from European countries having made contacts with individuals through the ESSTS association. The patient support organisations Tourettes Action and Tourette Association of America had on their websites lists of TS patient associations around the world and the survey link was also sent to all of these contacts. The survey targeted both patients and parents. Respondents were asked to describe their relationship to Tourette Syndrome. Respondents had to choose between options—I have TS myself, I am a parent of someone with Tourette Syndrome, I am a family member, partner of someone with TS or other. Further instructions were given for adults who have TS as well as their children. They were asked to complete this questionnaire in regards to themselves first, then come back and complete it a second time if it is for their child.

In the first part of the survey, participants were asked about their age (minimum age of 18 years) and what country they lived in. In addition, they were asked what kind of research they would prefer into TS: (i) research on the cause of TS or (ii) research on how to treat TS or improve symptoms (see Table 1 in Supplement). Processing of personal data for research purposes falls under the general provisions of the Data Protection Act 1998, but because only limited personal data were collected (age of participant) in this survey, research ethics committee approval was not required.

Results

The online survey was open for 6 months (from 10/2017 to 04/2018) and 2269 responses were collected. English language responses were the highest category of respondents followed by Dutch and Norwegian (see Table 2 in Supplement). However, we received answers from people from all over the world including Japan, India, Reunion Island (in the Indian Ocean) and Mexico (see Tables 2 and 3 in Supplement).

Respondents' answers were analyzed in two different ways: (i) by the language version of the survey they had completed and (ii) by country, where respondents lived. Since this survey was intended to investigate data from European countries, we excluded all surveys from further analyses where respondents indicated to live outside Europe (independent of the language version they had used) (see Table 3 in Supplement).

The largest age category of respondents—including patients and parents—was 35 to 44 years old, with 18% of the people in this category being patients (see Figs. 1, 2). English language responses were the highest category of

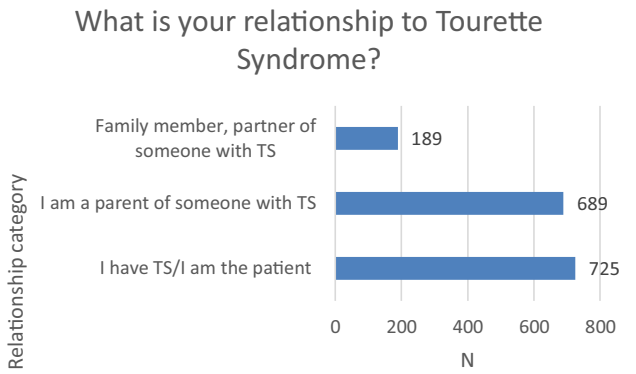

Fig. 1 Respondent categories from combined 13 language versions of survey ($N = 2269$)

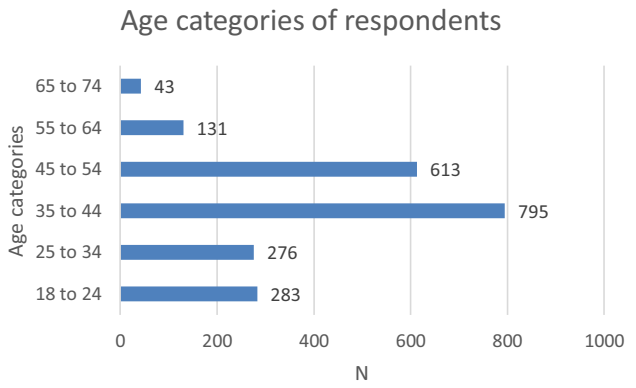

Fig. 2 Age categories of respondents from combined 13 language versions of survey ($N = 2269$)

respondents ($N = 535$) followed by Dutch ($N = 402$) and Norwegian participants ($N = 393$). The majority of the respondents were patients ($N = 725$) followed by parents ($N = 689$) as the second largest category of respondents (see Figs. 1, 2).

The survey was designed so that people could choose as many research priorities as they wanted. With respect to patient preferences on research topics: 71% of all respondents (combined together) would prefer research into how to treat TS and/or make symptoms better and 29% would prefer research into the cause of TS. When examining the patient-only responses, 64% of the patient respondents wanted research into the treatment, 36% wanted research into the cause of TS. Of the parent respondents, 74% indicated a preference for research into treatment, 26% wanted research into the cause of TS.

When asked what issues related to TS should be given research priority respondents indicated daily living issues (such as dealing with TS at home, work and school) as a top priority for research (28% of patients). Research on medication was a second priority (see Fig. 3).

Respondents were asked if they were aware of the variety of current treatment options for TS and if they had been offered any of them in their own country. Overall patients had a good awareness of the variety of treatments but there was a far lower frequency of these treatments being offered in their country (see Fig. 4). When asked which treatments had been offered to them, patients reported that most often medication followed by behavioural therapy was offered, followed, by a large gap, by cannabis, botulin toxin and deep brain stimulation (DBS) treatments being less likely to be offered overall.

As explained above, for the country-by-country analysis responses from outside Europe were excluded. Altogether 167 responses were excluded (7% of the total responses). Participants who completed the survey in a language which did not necessarily correspond to the country they were living in when they completed the survey were removed from parts of the analysis. As it was desirable to compare countries these people were removed from the analysis so as not to add a confounding factor to the results and make them uninterpretable. When there was a comparison between language speakers wherever they were their survey responses would have been included according to the language spoken.

For more details please refer to Table 3 in the appendix. In Fig. 5, data regarding knowledge about, and offer of, different treatment options are given for those 5 countries which had the most responses to the survey (see Fig. 5). Clear differences can be seen in both knowledge of treatment and whether treatments were offered to patients between the U.K., The Netherlands, Norway, France, and Italy. Certain trends in the responses are evident, with patients from The Netherlands seeming to have greater knowledge about cannabis, botulin toxin and DBS. Further details of the survey can be found here [11].

Discussion

The most prominent topic on research priorities for patients with TS in Europe is 'daily living issues' (such as dealing with TS at home, work and school); however, this aspect receives little attention in the regular treatment of tic disorders, which mainly focusses on tic reduction. Besides the tics, TS patients often have associated neuropsychiatric comorbidities such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), rage attacks, and sleep issues. Therefore the inclusion of the topic of daily living issues is very valuable and likely to be related to neurodevelopmental co-morbidities. These issues are often reported as a greater burden for patients than the tics themselves.

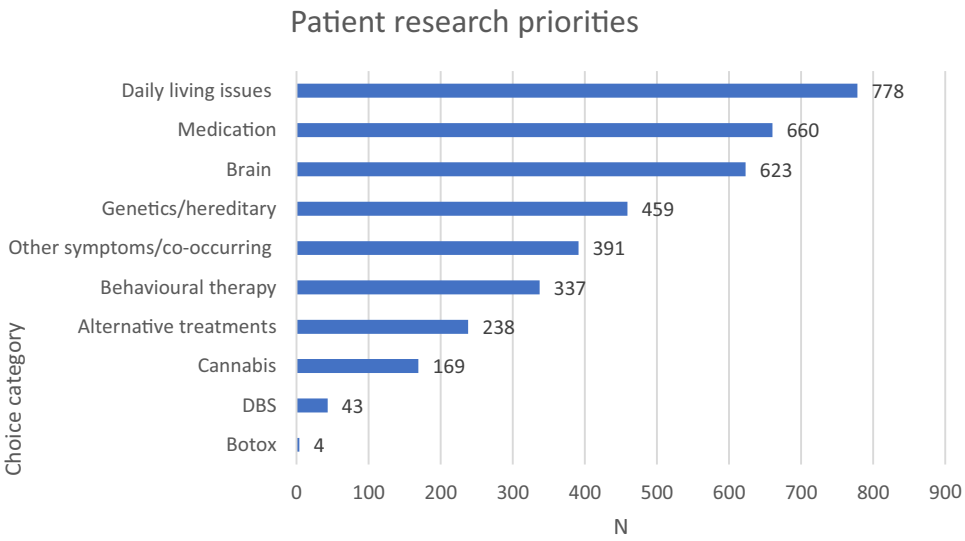

Fig. 3 Patient research priorities from combined 13 language versions of survey ($N = 2269$). *DBS* deep brain stimulation

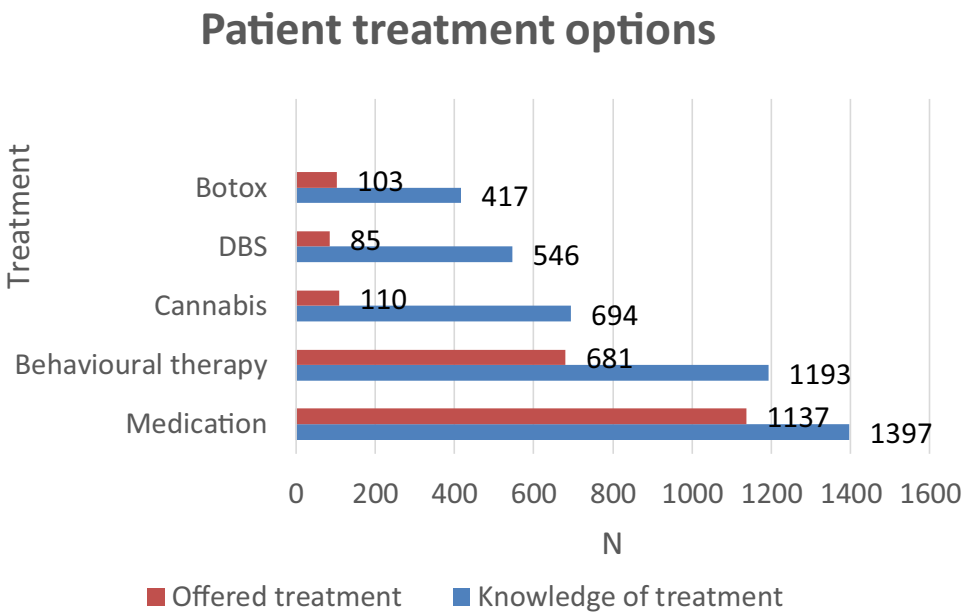

Fig. 4 Patient treatment options from combined 13 language versions of survey ($N = 2269$). *DBS* deep brain stimulation

Interestingly, results from the survey indicated that medication was the treatment option mostly offered to patients, despite the European clinical guidelines for Tourette Syndrome indicating that behavioural therapy should be offered as the first-line intervention for tics for both children and adult patients. This may reflect some of the challenges for patients to access trained therapists offering behavioural therapy for tics and a lack of trained therapists in various countries. Other treatments offered included cannabis, botulin toxin and DBS treatments being by far less likely to be offered overall. A trend seen in each of the countries selected was that patients often knew about treatments but had not been offered them.

Limitations

As in all survey research, we recognise that there are limitations in the methodology of the survey which should be acknowledged. This was a very simple survey containing seven questions only. Thus, some questions might have been too broadly formulated to be fully informative. Another criticism is that translations into 13 languages were not done by professional translators (although they were checked by a local TS representative in each country) and, therefore, there might have been issues of accuracy or patients' understanding of the survey questions. Further, because the link was sent to the patient

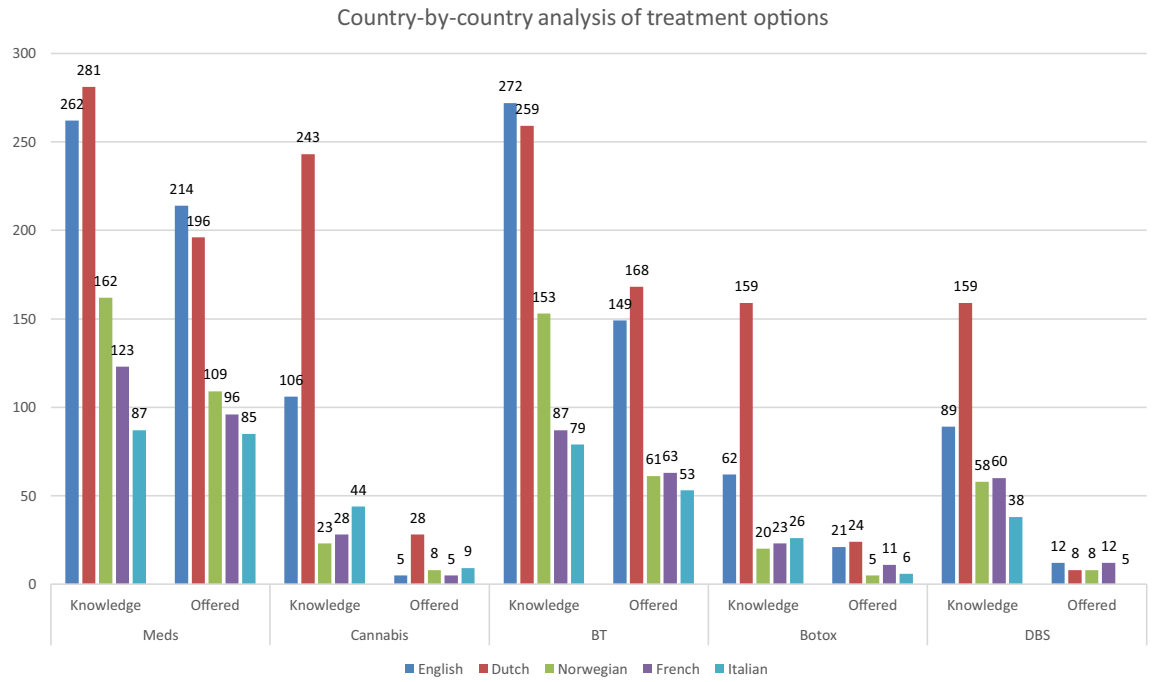

Fig. 5 Country-by-country analysis of treatment options ($N = 2269$). *Meds* medication, *BT* behavioral therapy, *DBS* deep brain stimulation

association representatives in the European countries, there was little control over to whom the survey was sent. One country, Sweden, refused to take part in distributing the survey because cannabis use is illegal in the country and, therefore, the local TS representatives felt that answers to this question would be unreliable, or unsafe to answer, and therefore they could not circulate the survey. A weakness in the survey was that Cannabis treatment was mentioned as a treatment on its own and also as part of other or alternative treatments thus making the interpretation of the responses about cannabis difficult to quantify.

Due to the multiple languages involved the researcher was limited to using closed questions. There was no budget or financial support for this study and the researcher did not have the capacity to collate, translate and analyse qualitative responses to open-ended questions. Although this would have been a rich source of data, there was no capacity to deal with any responses of this nature. In a follow-up study, it would be interesting to expand the answer options or (if feasible) include open questions, to explore what other wishes and themes patients mention. However, if this was to be done in multiple languages it could provide quite a logistical challenge and funding and time investment would be required.

Conclusions

The patients' perspectives survey on research and treatment is the first of its kind on a European scale for TS. Conclusions that arise include the recommendation to initiate more research into better treatments and problems in daily life of patients with TS. To increase the accessibility of behavioural therapy for patients and also encourage the training of healthcare professionals in this treatment. The wider implications of the research findings are that patients and carers are more interested and invested in treatment research that benefits them directly in their day-to-day lives which is an important message to emphasize to clinicians and researchers. It can be argued, however, that a breakthrough in pathology could potentially result in the greatest impact on reducing day-to-day mental health and burden from this condition. Therefore, we can put forward the suggestion that in reality both treatment and causes are required areas of research to pursue. The focus of research may favour aetiology and, therefore, this increases the importance of the research reported here with patient surveys evoking a discussion of the interplay between expectations, motivations and realities in terms of the different stakeholder views.

In terms of clinical implications of this research an important point moving forward is to see TS as part of the neuro-developmental spectrum including ADHD, ASD and OCD. It can be argued that to serve this patient population better, healthcare services could improve by moving towards specialist neurodevelopmental centres which can better manage these day-to-day patient realities. There have been great advances in expertise in the clinical treatment and management of conditions such as ADHD and ASD with increasing accessibility of treatment and clear

clinical pathways and, in some countries, guidelines such as The National Institute for Health and Care Excellence (NICE) in the UK. Patients may have the opportunity to be referred to a centre of expertise where they can access healthcare professionals with experience of diagnosis and treatment of tics and tic disorders. However, accessing this tertiary care is not possible or feasible for all patients. For example, children with both ADHD and TS (which is very common) may get different treatment options depending on whether they present at a TS clinic or an ADHD clinic.

A wider question is how we can bridge research and clinical work, and include patient participation to help in the treatment and management of TS as well as research. When considering this survey and a wider research context there are broader implications to be considered. The creation, distribution and collation of the survey data demonstrate it is feasible to survey large numbers of patients and carers across a continent. If it became readily achievable for clinicians and researchers to communicate or gauge patient opinion, this could be a valuable resource and should be further developed. This survey was created, translated into different languages and distributed with no budget or financial support. The main author liaised with all the patient associations in the different countries to check the language before the survey links were disseminated to patients in those countries. An interesting point is that after the survey links were distributed to the contacts in each country there was no/little control or management over how, or if, the survey links were distributed. There was one country, where although the translation was created and verified, the survey was not distributed to patients in that country due to conflict around mentioning cannabis in the survey. Therefore, future studies may wish to take into account cultural and political factors of different countries when designing surveys. With funding and investment, this survey could be greatly improved and its reach increased. It already represents an important step towards improving knowledge and care that meets the needs of patients by targeting a large patient and carer cohort across a continent spanning multiple languages. The collection of patient and carer opinions is highly relevant and likely to be important in the direction of travel of future medicine and the methodologies involved in this study are a good exemplar of the starting blocks of where research could be taken in future. The future evolution of digital technologies may allow these techniques to grow exponentially in future. It is also thanks to the developers of the European guidelines who recognize the value of patient participation in research by including this statement and thus make an important contribution to the further development of this new collaboration.

Patient involvement in research is the way forward with researchers seeking funding for their projects increasingly required to include PPI in all aspects of their research from design to dissemination. Researchers would benefit from stronger evidence showing the costs, benefits, and risks of engaging in PPI to mitigate it being regarded as 'a tick box approach to obtaining grants' [16]. The best model for involving patients in research and staying true to the PPI core tenant is that it should be a genuinely joint enterprise with patients empowered in all aspects of the research process and on an equal footing with other stakeholders [17].

The idea of having patients as research partners, involving them as equal members of a research team alongside the professional researchers, bringing their experiential knowledge to every phase of the research project, has already been suggested in other areas of medicine [1, 5, 12]. It can be seen as a very positive collaboration when 'experiential and professional knowledge can complement and influence one another' [13]. One of the ethical arguments for including patients in research is that the end users should always be involved in the development and research phases, as the main goal is to benefit them (summed up in the phrase often used by disability rights groups 'nothing about us, without us'). The main goal of shared decision-making as part of evidence-based medicine is to improve treatment through improved research. Additional side benefits could include patients' motivation to participate in research and treatment compliance. Another result of collaborating with patients in all stages of the research process is the potential to improve the quality, relevance, and uptake of research, as well as implementation of results [14]. By including patients in the research process there is 'greater centricity of patient experience' which 'accommodates greater power sharing between researchers and end-users of research' [15].

A leap forward in terms of patient voice is the formation of a new umbrella organisation called Tics and Tourette Across the Globe (TTAG) representing Tic and Tourette Syndrome (TS) patient associations around the world. It is anticipated that this association will be registered in 2021–22. This group of patient association representatives has already produced a guidelines leaflet for researchers with recommendations to ensure patient benefit regarding patients' involvement in research (see Fig. 6 in appendix). The authors of this paper absolutely recognise the generous and valuable invitation by the developers of the European guidelines to contribute to these guidelines. These are exciting steps forward as it reflects the increasing collaboration between patients and researchers. This initiative of patient inclusion has influenced and led to other collaborations where we have seen for the first time a chapter on patients associations around the world being included in a clinical textbook on Tourette Syndrome https://tinyurl.com/tfnjca68 (updated version in press 2022 edited by Davide Martino and James F. Leckman). As well as the creation of an

online TS patients association directory found on the ESSTS website https://www.essts.org/directory

One of the main aims of TTAG is to have an ongoing, mutually beneficial relationship between patient groups and researchers. TTAG looks forward to opportunities for a debate about the role, opportunities and challenges of the involvement of TS patients in research.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Code availability Not applicable.

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LETTER TO THE EDITOR

Treating Tourette syndrome and other chronic tic disorders: updated guidelines by the European society for the study of Tourette syndrome (ESSTS)

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This edition of the *European Child & Adolescent Psychiatry* contains updated guidelines for the clinical management of adults and children with Tourette Syndrome (TS). TS and other chronic tic disorders together affect 1% or more of the European population, and may lead to emotional distress, physical pain, lower quality of life, and for many, functional impairment [1–4]. Tic disorders begin in early childhood, and for a substantial number of individuals, persist into adulthood. While TS is defined by the presence of motor and vocal tics, among those who present for clinical care, comorbid psychiatric disorders are the norm rather than the exception [5].

The two articles that cover pharmacological and behavioral management of TS, respectively, and are written by leading European experts and members of the European Society for the Study of Tourette Syndrome (ESSTS), manage to be rigorous and comprehensive, all while having the tone and feel of a one-to-one consultation between clinicians. The reviews assess the current prescribing practices of expert clinicians who routinely treat TS, and combine these with a review of the literature to arrive at treatment recommendations that are practical in nature and sensitive to current clinical settings and constraints. This work builds on and updates the parameters outlined in the TS Practice Guidelines published by the American Academy of Neurology (AAN) in 2019, which represents a synthesis of studies conducted prior to 2018 [6].

The ESSTS and AAN guidelines have substantial overlap in content and scope, and are largely consistent with one another. However, the ESSTS guidelines as presented here do differ from the AAN guidelines, in part because additional studies have been published in the time since the systematic review conducted by the authors of the AAN guidelines, in part, because of differing availabilities of and indications for pharmacological agents in the United States compared to Europe, but most importantly because of ESSTS' clear focus on actual current clinician practice as a benchmark. For example, while both the AAN and the ESSTS guidelines discuss the need to assess for and treat co-occurring psychiatric comorbidities, more attention is paid to these comorbidities in the ESSTS guidelines, as well as to the off-target effects that pharmacological agents typically used to treat tics may have on other psychiatric symptoms. Pharmacological treatment of tics, while similar in scope and content, differs somewhat in order of choice between the two publications. For example, in the AAN guidelines, which focus on medications available and commonly used in the United States, alpha agonists such as clonidine and guanfacine are presented as the first line treatment for tics, while in the ESSTS guidelines published here, a second generation antipsychotic, aripiprazole, is the first line treatment.

Similarly, while the AAN guidelines focus on Habit Reversal Therapy (HRT), and in particular on a specific form of HRT called Comprehensive Behavioral Intervention for Tics (CBIT), the ESSTS guidelines also discuss the evidence for and use of another form of behavioral therapy: exposure and response prevention (ERP) for the treatment of tics. This addition is of relevance not only because of additional data suggesting its efficacy, but also because providers in Europe and elsewhere are more likely to be familiar with the principles and practices of ERP than they are with those of HRT, as ERP is a gold standard treatment for obsessive compulsive disorder (OCD) and for anxiety disorders, which are highly prevalent disorders that frequently co-occur with TS. Thus, it is reasonable to assume that ERP may be readily modified for tics by clinicians who have experience with using it to treat OCD or an anxiety disorder. Experience

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with HRT and CBIT, in contrast, has remained largely the purview of clinicians who specialize in treating TS and other tic disorders, and access to these forms of treatment may be more limited. Group treatment is also discussed as a potentially effective form of providing behavioral treatment to individuals with TS in the ESSTS guidelines—group treatment has the potential not only to increase access to care, but also to enhance off-target effects of behavioral interventions (increased school attendance rates, for example, as was found by Dabrowski et al. [7]).

The guidelines presented here by the ESSTS are timely, informative, and practical, with a focus on what clinicians with expertise in the assessment and treatment of TS are doing in their own practices, placed in the context of the most recently available data on the efficacy, safety, and long-term outcomes of each treatment discussed. They are anchored in what is currently known of the underlying mechanisms of action, and the potential risks and benefits of each form of treatment discussed. However, it is important to note that the ESSTS guidelines, like those previously published by the AAN, acknowledge that for TS, there is no single best treatment; instead, appropriate management must be individualized, guided by symptom severity, clinical presentation (including the presence and type of psychiatric comorbidities), patient preference, and resource availability. As with all neuropsychiatric disorders, the meta-message is that, although specific choices may differ between clinicians, the underlying principle remains the same: providers must carefully assess the clinical presentation and needs of the patient sitting before them, and develop a specific treatment plan that is individualized to their needs and preferences, based on the best that science currently has to offer.

Declarations

Conflict of interest None to declare.

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REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part I: assessment

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Abstract
In 2011 a working group of the European Society for the Study of Tourette Syndrome (ESSTS) has developed the first European assessment guidelines for Tourette syndrome (TS). Now, we present an updated version 2.0 of these European clinical guidelines for Tourette syndrome and other tic disorders, part I: assessment. Therefore, the available literature has been thoroughly screened, supplemented with national guidelines across countries and discussions among ESSTS experts. Diagnostic changes between DSM-IV and DSM-5 classifications were taken into account and new information has been added regarding differential diagnoses, with an emphasis on functional movement disorders in both children and adults. Further, recommendations regarding rating scales to evaluate tics, comorbidities, and neuropsychological status are provided. Finally, results from a recently performed survey among ESSTS members on assessment in TS are described. We acknowledge that the Yale Global Tic Severity Scale (YGTSS) is still the gold standard for assessing tics. Recommendations are provided for scales for the assessment of tics and psychiatric comorbidities in patients with TS not only in routine clinical practice, but also in the context of clinical research. Furthermore, assessments supporting the differential diagnosis process are given as well as tests to analyse cognitive abilities, emotional functions and motor skills.

Keywords Tics · Tourette syndrome · Assessment · Scales

Introduction

According to DSM-5, tics are defined as sudden, rapid, recurrent, non-rhythmic movements or vocalisations usually appearing in bouts while waxing and waning in frequency, intensity, number, complexity, and kind of tic [1]. Tic disorders including Tourette syndrome (TS) typically first appear in childhood, mostly between age 5 and 6 years [2]. TS encompasses the combination of chronic (more than 1 year) motor and vocal tics. Although the diagnosis of TS is in most cases straightforward, the condition is often underrecognised and many patients receive the correct diagnosis many years after the onset of symptoms. In these cases, delayed access to appropriate treatments both for tics and for commonly occurring neuropsychiatric comorbidities such as obsessive–compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD) may hamper psychosocial development and negatively impact quality of life. Therefore, both early recognition of tics and appropriate assessment of neuropsychiatric comorbidities, even those subclinical, are mandatory steps in the evaluation and treatment of patients with TS [3].

In 2011, experts of the European Society for the Study of Tourette Syndrome (ESSTS) have developed the first European guidelines in four parts [4–7]. Here, we present a revised and updated version of the original 2011 European Guidelines part 1: assessment. With these guidelines, we offer practical aids for clinicians from the neighbouring fields of psychiatry, neurology, paediatrics and psychology on how to assess the various characteristics of patients with tic disorder.

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Methods

For the new version of part I of the European clinical guidelines, we conducted a literature search, primarily aiming at detecting relevant research on the assessment of tics as well as co-existing comorbid conditions, and on quality of life, published after first guidelines between January 2011 and May 2021. Our systematic approach was based on the search in PubMed, Ovid, Web of Science, Embase, and APA Psych Info conducted on March 2020 and again on May 31, 2021. We searched for articles reporting about assessment of tics and TS using the search terms "tics" AND/OR "Tourette" AND/OR "assessment" AND/OR "scales" AND/OR "quality of life" AND/OR "OCD" AND/OR "ADHD" AND/OR "depression" AND/OR "anxiety". Reviews and meta-analyses in the area were further searched for relevant citations. In addition, the reference lists of the articles identified were reviewed for additional studies. In addition to the studies identified through systematic review, to make the publication list as comprehensive as possible, studies still in press and not officially published were added by the authors (i.e. through precedent knowledge about relevant publications). The methodology of the ESSTS survey is presented in a summary paper in the current issue of this journal Epidemiology of tics and tic-related comorbidities.

Prevalence

TS affects between 0.3 and 1% of the general population [8–10], depending on the age of the study group and rigorousness of the sampling method used in the research. Tics occur predominantly in young people (before age 18), and typically have a waxing and waning course [11]. Tics occur more often in boys than in girls, with a male to female preponderance of between 3:1 [12] and 4.3:1 [13, 14], but in adult patients with TS this male preponderance is less pronounced [15]. Both genetic and individual environmental factors contribute to the tic/TS phenotype [16–22].

Course and course prediction of tics and comorbidities

The mean age at onset is around 5 years although lower ages at onset are reported in up to 40% of patients [23]. In children and adolescents, waxing and waning is the rule, whereas, in adults tics tend to run a more persistent course [24]. Complex tics generally present later than simple ones, with vocal tics often appearing 1 or 2 years later than motor tics [25], although in some patients vocal tics appear first [26]. For most patients, the worst period of tics occurs between 8 and 12 years of age [27, 28]. 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 10 years of age, experience a significant tic decrease during adolescence. By 18 years of age tic intensity and frequency has decreased to such an extent that the majority of people no longer experience significant impairment from tics, although most individuals still have mild tics [29]. Yet, a small proportion of patients does not experience a clinically meaningful decrease in tic intensity, and others continue to experience a severe and debilitating form of tic disorder [25]. Reports on whether certain types of tics in childhood predict tics or comorbidity in adulthood are somewhat conflicting [24, 30–33]. Recently it has been shown that tics, obsessive–compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD) severity in childhood were related to high tic scores, OCD or ADHD diagnoses in early adulthood [34] but longitudinal studies remain rare and replication is needed.

Diagnosing

Classifications

Since the original guidelines were published, the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) and the eleventh revision of the International Classification of Disease (ICD-11; WHO, 2019) have been published. Both include changes to the classification of tic disorders. Table 1 provides an overview of the differences between DSM-5 and ICD-11 classification. In DSM-5, tic disorders are classified as 'motor disorders' within the neurodevelopmental disorders category that also includes intellectual disabilities, communication disorders, autism spectrum disorders (ASD) and ADHD. Within the motor disorders category, tic disorders are grouped alongside developmental coordination disorder and stereotypic movement disorder. The diagnostic categories for tics include Tourette's disorder (307.21), persistent (chronic) motor or vocal tic disorder (307.22) (with prevalence of 3–9% [35]), provisional tic disorder (307.21), unspecified tic disorder (307.20) and other specified tic disorder (307.20). Importantly, just recently, it has been suggested that all these disorders belong to the same spectrum, TS being the most severe one [36].

Compared with previous DSM-IV-TR classifications, the definition of tics has been refined, and the term *stereotyped* to distinguish between stereotypies and tics has been removed. The duration criterion of a tic-free period of less than three consecutive months has been omitted for the chronic tic disorders. Provisional tic disorder replaces transient tic disorder, because a transient nature of tics can only be defined retrospectively and initially presenting tics

Table 1 Differences between DSM-IV-TR, DSM-5, ICD-10, ICD-11

	Labels	Parent category	Criteria of TS	Criteria of chronic/persistent vocal and/or motor tic disorder	Criteria of provisional/transient tic disorder
DSM-IV-TR	Tourette's disorder; chronic motor or vocal tic disorder; transient tic disorder; tic disorder not otherwise specified	Disorders of infancy, childhood, and adolescence	Multiple motor and one or more vocal tics at some point in illness Tics occur daily or periodically, but 1 year since onset, and no tic-free period of more than 3 consecutive months Onset before 18 years Not caused by substance or other condition	One or more motor or vocal tics present at some point, not both motor and vocal symptoms Tics occur daily or periodically, but 1 year since onset, and no tic-free period of more than 3 consecutive months Onset before 18 years Not caused by substance or other condition No history of TS	One or more motor and vocal tics Tics occur daily or periodically, but for 4 weeks and 12 months Onset before 18 years Not caused by substance or other condition No history of TS Specify if single episode or recurrent
ICD-10	Combined vocal and multiple motor tic disorder (de la Tourette); chronic motor or vocal tic disorder; transient tic disorder; other tic disorders; tic disorder, unspecified	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	Multiple motor and one or more vocal tics, not necessarily occurring at the same time	One or more motor or vocal tics, but not both types Symptoms occur 12 months	One or more motor and/or vocal tics Symptoms occur 12 months
DSM-5	Tourette's disorder; persistent (chronic) motor or vocal tic disorder provisional tic disorder; other specified tic disorder; unspecified tic disorder	Neurodevelopmental disorders	Multiple motor and one or more vocal tics at some point in illness May wax and wane, but have persisted 1 year since onset Onset before 18 years Not caused by substance or other condition	One or more motor or vocal tics present at some point, not both motor and vocal symptoms May wax and wane, but have persisted 1 year since onset Onset before 18 years Not caused by substance or other condition No history of TS Specify if motor tics only, vocal tics only	One or more motor and/or vocal tics Tics present for 1 year since onset Onset before 18 years Not caused by substance or other condition No history of TS or persistent tic disorder
ICD-11	Tourette syndrome (combined vocal and motor tic disorder); persistent (chronic) motor or phonic tics; provisional tic disorder; substance-induced tic disorder; tic disorder due to general medical condition	Disorders of nervous system—primary; mental and behavioural disorders—secondary; obsessive–compulsive and related disorders; neurodevelopmental disorders	One or more motor and/or vocal tics occurring over the same period of time Symptoms occur 12 months	One or more motor and one or more vocal tics Symptoms occur 12 months	One or more motor or vocal tics, but not both types Symptoms occur 2 weeks and 12 months

For the previous version of this Table, refer to the 2011 ESSTS Guidelines [4]

DSM-IV-TR The Diagnostic and Statistical Manual of Mental Disorders Text Revision 4th edition, *DSM-5* The Diagnostic and Statistical Manual of Mental Disorders 5th edition, *ICD-10* the International Statistical Classification of Diseases and Related Health Problems, 10th edition, *ICD-11* the International Statistical Classification of Diseases and Related Health Problems, 11th edition

may eventually be diagnosed as chronic tic disorder. The category of persistent tic disorder has been specified, i.e. at least one vocal or two motor tics should be present, to distinguish between vocal and motor tics that are chronic. The unspecified and other specified tic disorder categories have additionally been introduced to replace tic disorders not otherwise specified, to account for tics with onset in adulthood or tics triggered by other medical conditions or use of medications and drugs. Stimulant use as a specific cause of tics has been removed.

In ICD-11, TS is removed from the category of emotional disorders and classified under the category of movement disorders. In our opinion this is in disregard of the growing body of evidence pointing into the positioning of tics and TS as a psychiatric and emotional disorder (for more details consult the "European clinical guidelines for Tourette Syndrome and other tic disorders. Summary statement" in the current issue of this journal).

Characteristics of tics

Tic characteristics have been described in detail in the 2011 assessment guidelines and are summarised in Table 2. Because of their importance to the clinical assessment process, here the key points are summarised: (1) tics are either motor or vocal in nature. Motor tics reflect brief, sudden, irresistible, inapposite and non-rhythmic recurrent movements in voluntary muscles or muscle groups. Vocal tics reflect sounds elicited by a flow of air through the vocal cords, mouth or nose; (2) tics are often associated with essential characteristics that distinguish them from other hyperkinetic movement disorders, which include (i) suggestibility by environmental cues, (ii) a preceding premonitory urge or tension, (iii) mostly a feeling of voluntariness when performing the tic, and (iv) the ability of temporary suppression that is often accompanied by an inner tension.

These features vary across patients with differing levels of suggestibility, premonitory urges and suppressibility that are in part related to age and tic severity [37]. In addition, the same tic burden may be associated with different intensities of premonitory urges [36, 38–40]. The distribution of premonitory urges often co-varies with the distribution of tics [41]. Higher levels of premonitory urges have been reported to be associated with greater awareness of tic expression, with only moderate to low associations between subjective and objective measures of tics [42]. Clinical experience shows that most people with tics are not aware of all of their tics. Most typically, mild simple motor tics such as eye tics may escape patients' attention. Accordingly, some individuals report that they are "tic-free" despite the presence of mild tics on video recordings [40].

Since the publication of the first version of the ESSTS guidelines [4] there has been also a growing interest in the cognitive and sensory characteristics of tics and the role of attentional processes [43–45].

Role of genetics in the diagnosis of tic disorders

From family studies it is well-known that (a history of) tics is presented in a substantial proportion of parents [9] and that patients' first-degree families have a higher risk of developing tics, obsessive–compulsive symptoms (OCS) or ADHD compared to healthy control families [46]. Accordingly, three epidemiological twin- and family studies and two genome-wide association studies (GWAS) have shown heritability estimates ranging between 28 and 56% [47–51], with the remaining variance being explained by unique environmental factors. Interestingly, a recent large GWAS

Table 2 Different types of tics and their characteristics

Type of tic	Typical features
Motor	Arise in the voluntary musculature and involve discrete muscles or muscle groups
Vocal	Consist of any noise produced by movement of air through the nose, mouth or pharynx
Stimulus-bound	Occur in response to internal or external stimuli (visual, phonic, tactile or mental)
Blocking	Motor or vocal tics that interrupt the voluntary action without alteration of consciousness (dysfluency of speech or gait)
Simple	Are restricted to one muscle or a single muscle group (e.g. eye blinking, nose twitching, tongue protrusion), simple, meaningless sounds (e.g. grunting, throat clearing, coughing, sniffling and barking)
Complex	Involvement of more muscle groups (e.g. repetitive touching of objects or people, repetitive obscene movements (copropraxia), mimicking others (echopraxia) complex vocal tics are words or phrases, expressing obscenities (coprolalia), repeating others (echolalia) or repeating oneself (palilalia))
Clonic	Last less than 100 ms
Dystonic	Last more than 300 ms Repetitively abnormal posture of a kind that one may see in dystonia
Tonic	Last more than 300 ms Relatively long duration of the contraction (in e.g. back muscles) without exhibiting abnormal postures

meta-analysis suggested that TS and other primary tic disorders share the same polygenic risk [16].

Genetic complex trait analysis (GCTA) revealed that single-nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) < 5% seem to explain 21% of the variance in TS [52].

Although variants in different TS risk-genes have been identified (e.g. CNTN6, NRXN1, SLITRK1 and HDC), they are responsible for genetic vulnerability only in a very small proportion (about 1%) of TS affected individuals [53]. Other findings from recent GWAS such as a genome-wide significant locus within the brain-expressed gene FLT3 on chromosome 13 could not be replicated [16, 50]. Thus, there is no doubt that in TS, both genetic and environmental factors contribute to the onset and persistence of the disease. Despite that, to date, no specific genetic markers have been identified.

Tic-related phenomena

The clinical presentation of TS includes a range of tic-related phenomena that have been extensively studied in recent years due to their impact on daily functioning for individuals with TS.

Compulsive tics/tic-like behaviours and impulsive tics

Complex motor tics often have a compulsive nature and can be indistinguishable from goal directed or OCD-like behaviours, for example when a tic is repeated until a "just-right feeling" is achieved. Common compulsive tics of this nature include repeated touching, tapping and evening-up (e.g. brushing against something on one side and then the other). For some individuals these compulsive tics/tic-like behaviours are performed a fixed number of times and/or aim at neutralising an anxiety-driven worry (often about preventing harm). However, for the majority of individuals they are not anxiety-driven worries, but instead are performed to satisfy a feeling of sensory discomfort with engagement until a 'just right' feeling is achieved [54]. Interestingly, the commonly reported "non-just-right"-feelings that accompany symmetry behaviour in TS has a parallel with the premonitory urges preceding tics in TS [55].

Self-injurious behaviours

Self-injurious behaviours (SIB) are highly associated with complex motor tics and coprophenomena in patients with TS, can occur in response to provocative stimuli in the outside world rather than OCD or OCS [37]. However, self-injuries in patients with TS are not only associated with tics, but also with a number of other co-occurring symptoms. These include hyperactivity and accident-proneness in the scope of ADHD, rage attacks or excessive washing or grooming resulting in skin lesions in patients with co-occurring OCD [56].

Quality of life in TS

Children and adolescents with tics experience a poorer quality of life than healthy children [57], with poorer quality of life related to increased tic severity [58] and mostly associated with comorbid ADHD and OCD [58–61]. However, their overall quality of life is better than in youth with other psychiatric disorders. Poor quality of life in adults with TS, is associated with the presence of comorbid OCD and depression and to a lesser extent with tic symptom severity [58]. The effect of anxiety and OCS severity on quality of life is often mediated by depression severity [58].

Comorbidities

In the following paragraph we want to address clinically important and in particular new aspects related to comorbidities in TS.

OCD and ADHD

Obsessions and compulsions occur in between 22 and 66% of clinical TS populations [23, 62] and are, together with ADHD (occurring in 55–60%) the most prevalent comorbid disorders in patients with TS. Especially the OC symptom dimension of symmetry and non-just-right behaviour is highly prevalent in TS [63], but all other OCD symptom dimensions including checking, ordering and washing occur as well. Interestingly, hoarding behaviour has been found to have genetic overlap both with TS, OCD and ADHD [64]. In patients with TS and comorbid ADHD it can be difficult to differentiate tics from fidgetiness and hyperactivity. However, tics are repetitive and patterned movements that alternate completely normal motor patterns, which clearly distinguish them from overall behavioural hyperactivity and restlessness. Comorbid ADHD is associated with increased rates of OCD, anxiety, anger control as well as personality and mood disorders [62, 65, 66].

Autism spectrum disorder (ASD)

Only recently attention has been directed towards relationships between TS and ASD, with two studies of TS patients and family members, and one comparative study between TS, ASD and general population subjects [67–69]. All

participants completed several quantitative self-reports on autistic personality traits, including subscales on restrictive and repetitive behaviours. Overall, up to 22.8% of children with TS met cut-off criteria for ASD (22.8%), but only 8.7% of the TS adults. The elevated rate in the studies in children was primarily due to high scores on the Social Responsiveness Scale (SRS) Repetitive and Restricted Behaviours (RRB) subscale, which bears striking resemblances with OCD symptoms. Specifically, children with clinicians' diagnosis of TS plus OCD exhibited elevated SRS scores indicating symptom overlap between assessments of OCD and ASD on this scale. Fully in line with these results, the two studies in TS adults investigating underlying factor structure across scales on tics, OC symptoms, ADHD and autistic symptoms [59, 68] revealed strikingly similar results, with one overlapping factor between OC and autistic symptoms, defined by the numbers and patterns subscale of the autism self-report.

Rage attacks

Episodic impulse control disturbances and anger control problems (commonly referred to as 'rage attacks') are reported in 25–75% of patients with tic disorders. The episodes are described as abrupt outbursts of verbal or physical aggression generally directed at persons in the vicinity of the patient. The episodes are seen as being in excess of the response required of the eliciting stimulus [70]. Rage attacks are often associated with comorbid disorders such as ADHD, ASD, emotional liability, affective dysregulation characteristic for disruptive mood disorder and OCD [71], but also occur in a proportion of patients with "TS only" without any comorbidities. Budman et al. used the newly developed "Rage Attacks Questionnaire" (RAQ) to assess rage attacks in children and adolescents [72]. While they suggested that episodic rage in TS represents a nonspecific symptom, in a recent study in adults using a revised version of this scale (The Rage Attack Questionnaire-Revised, RAQ-R) [73], it could be demonstrated that rage attacks are significantly more common in TS compared to controls and can be clearly differentiated from impulsivity as indicated by a low correlation between the RAQ-R and established rating scales for impulsivity. Although rage attacks occurred more often in individuals with comorbid ADHD, they were also found in patients with "TS only", independently from comorbid ADHD, impulsivity, and OCD. Rage attacks were found to negatively influence patients' quality of life [73].

Neuropsychological impairments

Children with TS are at risk of academic underachievement, grade retention and are in the need for additional support [74], particularly those with more severe tics and co-existing conditions [75]. In addition, the prevalence of tics in children with special educational needs is as high as 28% [76]. Adults with TS can suffer from neurocognitive difficulties, which impact on their daily function [77]. The literature on neurocognitive impairments is somewhat contradictory, as study samples differ with respect to age (children vs adults) and comorbidity patterns, with the consequence of different cognitive profiles [78–80]. Intelligence is generally considered to fall within the average range in individuals with TS. As an exception, a Danish paediatric clinical cohort of children with TS reported lower non-verbal and full-scale intellectual efficiency (less than one standard deviation) in comparison with a control group, which correlated with disease duration and presence of co-occurring conditions [81]. The authors concluded that early onset of tics (and not disease duration) might be associated with specific deficits of cognitive performance. Difficulties with motor skills [82] and visual perceptual abilities [83] are also reported. Specific learning disorders are also known to be frequent in children with TS [75], particularly difficulties with mathematics and handwriting [84–86]. Although the literature is inconsistent, there is some indication that executive dysfunction in TS is specifically related to reduced inhibitory control [87] and cognitive flexibility [88]. Impairments in sustained attention, working memory, habit/procedural learning, and social cognition are also found; deficits are often stronger in the presence of comorbid ADHD or OCD [89–92] (for review see [87]). In adults executive dysfunction has been found in persons with "TS only" even in the absence of co-occurring conditions [93]. Hypothetically, the adult clinical group represents a more severe group of patients with persistent tics.

Interestingly, some studies have found enhanced abilities in TS patients with respect to inhibitory control [82, 94], procedural memory [95], and habit formation [96]. Inhibitory control seems to improve over time and be less disabling in adulthood, in parallel with tic severity decrease [97].

Differential diagnosis

Other hyperkinetic movement disorders

The distinction of tics from other hyperkinetic movements (e.g. dystonia, myoclonus and chorea), or vocalisations in the context of neurodegenerative disorders (e.g. repetitive vocalisations) or vocalisations as part of ictal phenomena [98] is in most cases straightforward. However, occasional brief motor tics could be mislabeled as chorea, whereas prolonged motor tics could resemble dystonic contractions. Specifically, eye squeezing as part of blepharospasm can resemble severe eye blinking tics. Most importantly, tics may co-exist with other hyperkinetic movements and in these cases, misdiagnoses are not uncommon [99, 100]. For

example, the association of tics with dystonia as a primary syndrome has been previously reported [101].

Stereotypies

One particular area of confusion in this regard involves stereotypies, which often, as neurodevelopmental phenomena, co-occur with tics. Stereotypies, like tics, are also non-goal directed movement patterns, but are repeated continuously, often quasi-rhythmically [102]. Importantly, stereotypies typically involve more muscle groups than tics (e.g. stereotypic repetitive movements of the trunk and arms/hands, and less common the legs or even come along with vocalisations) and they are most often phenomenologically fixed over longer periods of time. Stereotypies generally start at an earlier age than tics (between age 0–3 years), and, as aforementioned, are often encountered in children with tics or other psychiatric conditions (such as ASD), but may also be part of normal development. Both tics and stereotypies are distractible and suppressible, and the attenuation of stereotypies is less effortful and more instantaneous than tics. Importantly, different from tics, stereotypies are typically not associated with a premonitory urge, but their presence may exert soothing effects, sense of fulfillment or even joy and can come along with fantasy dreams [102–104].

Functional movement disorders and vocalisations

A challenging differential diagnostic category involves functional tic-like movements and vocalisations. There is a growing literature on functional movement disorders (FMD) and vocalisations, with prevalence rates ranging between 3% in population-based studies and 30% in neurological outpatient clinics [105, 106]. Functional tic-like movements are commonly encountered in specialist clinics for tics and TS. Indeed, over the past few years, several case series have documented the clinical features of these patients [107–111]. The first two reports focussed on a range of atypical features, such as absence of premonitory urges and the inability to voluntarily suppress tics, adult onset of symptoms, female preponderance of patients, as well as differences both in the types of tic movements or sounds and the somatotopy of body parts involved. For example, patients with functional tic-like movements most often exhibit rhythmic complex motor or phonic behaviours, which affect the arms, legs and trunk equally often—or even more often—whereas, in TS face, head or shoulders are primarily affected. Also, typical tics are fast, brief, phasic movements representing fragments of actions. In addition, at a given time, tic repertoire is usually limited and repetitive albeit not rhythmic. Following these first reports, it subsequently became clear that paediatric patients may present with functional tic-like movements as well [112] and indeed it is now recognised that the symptom overlap between patients with tics and functional tic-like movements may be greater than previously thought. Most importantly, both types of behaviours may co-exist in the same patients, although frequencies of co-occurrence are not known. Therefore, in such cases thorough clinical neuropsychiatric assessment in expert centres for tics and TS is warranted. Similarly, functional vocalisations are usually characterised by onset in adulthood, proceeding traumatic events, tendency to block speech and poor response to anti tic medication [111]. Moreover, coprolalia is much more common in functional vocalisations than TS, in which it is present in only 15–20% of patients [113, 114]. Ganos et al. [115] indicate that coprolalic words in patients with functional vocalisations differ from coprolalia in TS. Patients with functional coprolalia use longer and compound words or sentences and included an atypically high number of different swear words including words rarely encountered in TS. In contrast, coprolalia in TS is characterised by usage of short swear words, usually widely known.

Finally, in recent years there has been a growing evidence regarding functional tic-like behaviours induced by social media [116]. Some researchers postulate it could be, at least partially, due to overall increase of mental disorders due to COVID-19 pandemic [116].

Somatic conditions

Sometimes eye tics are misdiagnosed as ophthalmological conditions, conjunctivitis or dry eye syndrome. Further, patients with predominant vocal tics such as throat clearing or sniffing are sometimes first referred to otolaryngologists, when an allergy is suspected, or to a gastroenterologist to investigate on gastroesophageal reflux. Vocal tics can lead to speech blockade [117] and stuttering-like symptoms that may be misdiagnosed as tonic–clonic stuttering. Motor (or vocal) phenomena resembling tics might be due to focal epileptic activity. In these cases, the abnormal phenomena are characteristically focussed only on specific body parts and their manifestation is stereotypic. Sometimes specific triggers, like for example the presence of photic stimuli, can trigger the abnormal–epileptic–behaviours.

PANS/PANDAS

The hypothesised causal relationship between tic onset and course with streptococcal infections in children, conceptualised in the concept of Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS) [118, 119]), is a topic of debate. Importantly, a recent large scale collaborative effort across multiple sites in Europe (EMTICS) [119] on the relationship between β-haemolytic Streptococcal infections and tic exacerbation in children and adolescents with TS has indicated no specific relationship [120–122]. Instead, more generally

there is substantial evidence for involvement of immunological factors in tic onset and persistence. Moreover, treatment of children with either antibiotics or immune electrophoresis in whom a relationship with streptococcal infections was assumed has not proven efficacy to date [123, 124]. Finally, the phenotypic expression of tic onset as a result of PANS hugely overlaps with general tic onset phenomenology. As a consequence, the use of specific PANS-related scales does not seem to have added value to clarify the diagnostics of TS nor does it have consequences with respect to current treatment approaches. Therefore, we have chosen not to provide specific recommendations with respect to rating scales that measure PANS and Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)-related tic symptomatology.

Work-up

In the context of the updated ESSTS guidelines, we have conducted a survey among the members of the ESSTS working group to investigate, which assessments are most commonly used among specialists in the field (see the "European clinical guidelines for Tourette syndrome and other tic disorders. Summary statement" in the current issue of this journal for a thorough description). In each section of the work-up paragraph hereunder we have included results of the survey.

General evaluation

A general evaluation of both children and adults includes assessment of the most debilitating complaints and symptoms, assesses how the symptoms have developed and inquiries about potential stressors and triggers. Especially in children and adolescents, a developmental history is obtained, and family functioning is assessed including parental coping styles and parental conflict, social network and financial and housing situation. In adults, partner status, current work and financial/housing situation is assessed as well. Moreover, if available hetero-anamnesis on tics, OCD, ADHD family history and disease status is obtained from parents, partner or caregivers in the vicinity of the patient.

Physical examination

We recommend physical and particularly neurological examination, when clinically indicated to exclude other neurological diseases in addition to tics. Neuroimaging, EEG and further additional examinations do not add value in establishing the diagnosis of a tic disorder and therefore, should be performed only if clinically indicated. For further information please refer to the previous version of the guidelines [4].

Parent- and patient rating scales to support the general evaluation

In children, adolescents and adults, it is highly advisable to supplement clinical interviewing with screening of the most prevalent comorbid psychopathology by interviewing parents and children supplemented with self-report scales. For further details see Table 3.

Specific evaluation

Clinical interview

Age of onset of first motor and vocal tics are recorded as well as tic history, 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/injuries of muscles and joints), about somatosensory phenomena accompanying the tics (including character, location, and duration), tic suppressibility (including duration) and about exacerbating or relieving factors accompanying the tics (e.g. stress sensitivity) as well as specific complex tics including copro-, echo- and paliphenomena. Patients and parents are asked about the daily, weekly and monthly course of tic activity (including during sleep), to anticipate future treatment effect in relation to the patients' natural symptom fluctuations, and to clarify the psychosocial impact of tics on family functioning, learning and quality of life [146], and tic exacerbation.

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

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 tic severity on an individual and 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 [154] particularly of "tic attacks" or other exacerbations with potentially functional components. In particular, in those patients, who do not exhibit any tic during the consultation, video recordings can be very helpful. Moreover, mobile applications such as TicTimer [155] help to measure tic in more objective and comparable way.

Table 3 Tic and comorbidity assessment in children and adults

Topic	Measurement instrument children	Measurement instrument adults	Time (min)
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)	YGTSS	YGTSS	Max. 30
Tic symptoms	STSS	STSS	Max. 30
Tic symptoms	TODS	TODS	Max. 30
Tic symptoms	RVBTRS	RVBTRS	Max. 30
OCD symptoms (past/present)	CY-BOCS, CY-BOCS-II, OCI-CV, LOI-CV, CHOCI	Y-BOCS/D-YBOCS, OCI-R	Max. 30
ADHD	SNAP/CAARS (parent/teacher/self-rating), Qb + © DSM-5 criteria of ADHD [125] ADHD-RS	SNAP/CAARS, Qb + ©, Adult ADHD Self-Report Screening Scale for DSM-5 [126], WURS	Max. 50
Autism symptoms	Social Responsiveness Scale (SRS)	Autism Questionnaire (AQ)	Max. 25
Impulsive behaviour	BIS-15	BIS-15	Max. 5
Sensory premonitory urges	PUTS (10 items) I-PUTS (10 items)	PUTS (10 items) I-PUTS (10 items)	Max. 5 Max. 5
Course of psychopathology			
Severity-tics	YGTSS (11 items; current & worst ever; age at worst ever)	YGTSS (11 items; current & worst ever; age at worst ever)	Max. 15
Severity OC symptoms	CY-BOCS severity (2 9 10 items; current & worst ever)	Y-BOCS severity (2 9 10 items; current & worst ever)	Max. 10
Severity depression and anxiety	RCADS (47 items)	BDI/BAI (42 items)	Max. 20
Psychosocial functioning	CGI, GTS-QOL (28 items)	CGI, GTS-QOL (28 items)	Max. 17
Life events	Brugha (29 items)	Brugha (29 items)	Max. 15
Estimation of patients' time for the specific baseline measurements	Max. 175 min	Max. 165 min	

DCI Diagnostic Confidence Index [127], *DISC* Diagnostic Interview Schedule for Children [128], *Kiddie-SADS-PL* Schedule for Affective Disorders and Schizophrenia for School-Age Children [129], *SCID* Structured Clinical Interview on DSM-5 axis I disorders[130], *MINI* Mini International Neuropsychiatric Interview[131], *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale [132], *CY-BOCS-II* the Children's Yale-Brown Obsessive–Compulsive Scale Second Edition [133], *Y-BOCS* Yale-Brown Obsessive–Compulsive Scale [134], *DY-BOCS* Dimensional Yale-Brown Obsessive–Compulsive Scale [135], *SNAP-IV* Swanson, Nolan and Pelham questionnaire, 4th edition [136], *CAARS* the Connors ADHD Rating Scale, *RS* Social Responsiveness Scale [137], *BIS* Barratt Impulsivity Scale [138], *PUTS* Premonitory Urge Tics Scale [139], *I-PUTS* the Individualised Premonitory Urge for Tics Scale [140], *YGTSS* the Yale Global Tic Severity Scale [141], *RCADS* Revised Child Anxiety and Depression Scale [142], *BDI* Beck Depression Inventory-II [143], *BAI* Beck Anxiety Inventory [144], *CGI* Clinical Global Impression [145], *GTS-QOL* Gilles de la Tourette Syndrome–Quality of Life Scale [146], *Qb* + © Quantified Behaviour Test Plus [147], *OCI-CV* Obsessive Compulsive Inventory; child's version [148], *LOI CV* Leyton Obsessive Inventory Child Version; (in children)/LOI (in adults) [149], *WURS* the Wender Utah Rating Scale [150], *STSS Shapiro* Tourette-Syndrome Severity *Scale* [151], *TODS* Tourette's Disorder Scale [152], *RVBTRS* Rush Video-Based Tic Rating Scale [153]

Our recommendations on assessments for tics and comorbidities in patients with TS are mainly based on (i) our previous guidelines [4], (ii) a systematic review published in 2017 by the Movement Disorder Society based on experts opinion classifying tic rating scales as "recommended", "suggested" or "listed" [151] and (iii) a survey conducted among European and American ESSTS members in 2019 asking about current use of rating scales for tics.

In brief, the Movement Disorder Society recommends five scales for the assessment of tics, including severity, impairment and premonitory urges: the Yale Global Tic Severity Scale (YGTSS) [141], the Tourette Syndrome Clinical

Global Impression (TS-CGI) [156], the Tourette's Disorder Scale (TDS) [152], the Shapiro Tourette syndrome Severity Scale (STSSS) [157], and the Premonitory Urges for Tics Scale (PUTS) [139] and the Premonitory Urges for Tic Disorders Scale-Revised (PUTS-R) [158]. Six other scales were rated as "suggested": the Rush Video-Based Tic Rating Scale (RVTRS) [153], the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (the MOVES) [159], the Tourette Syndrome Global Scale (TSGS) [160], the Global Tic Rating Scale (GTRS) [151], the Parent Tic Questionnaire (PTQ) [161], and the Tourette Syndrome Symptom List (TSSL) [151]. Finally, two screening instruments on both tics and comorbidities, i.e. the Motor tic, Obsession and compulsions, Vocal tic Evaluation Survey and Autism-Tics (MOVES) [159] and the Autism-Tics, ADHD and other Comorbidities inventory (A-TAC) [162], were upgraded to the status of "recommended" while two other instruments (Apter 4-questions screening and Proxy Report Questionnaire for Parents and Teachers) were "suggested."

Interviews to establish the diagnosis

To establish the diagnosis of TS, the diagnostic criteria of the newest DSM-5 Tourette's disorder classification are used. According to the ESSTS survey, 94.3% of respondents use primarily an unstructured clinical interview to diagnose TS in clinical practice.

Ratings of tic severity

In addition, according to the recent ESSTS survey, 73.6% of clinicians use self-reported and/or interview-derived rating scales to support the diagnosis of a primary tic disorder and to list characteristics and severity of tics. Of these users, all clinicians used the YGTSS, which combines both the assessment of tics and impairment. Taking into account psychometric studies, based on the amount of research conduct on psychometric of the YGTSS, it can also be concluded that the YGTSS has the best evidence for assessing tic severity [163]. According to our survey, clinicians use the YGTSS both in daily clinical practice, as well as in research. In 2018, a revised version of the YGTSS (YGTSS-R) was presented based on a relatively large scaled psychometric study in children and adults [163]. Although the YGTSS showed excellent internal consistency and other psychometric properties, changes in anchor points were proposed for several items of the scale without changing the anchor point descriptions, to reduce the skewness in reporting of some of the items of the YGTSS. To give an example, the authors proposed new tic frequency description which is divided in five new categories: none, minimal, mild, moderate, marked and severe. Moreover, minimal frequency, which is equivalent to rare in the original YGTSS, is equivalent to tics present on a daily basis, which was not the case for the previous YGTSS edition. Importantly, Haas et al. [164] demonstrated acceptable psychometric quality of the YGTSS.

Other frequently used scales in clinical practice and research are self-assessments (Adult Tic Questionnaire (ATQ) [165], TSSL [151] and video assessments (Rush Video-Based Tic Rating Scale [153]). The scales recommended, suggested and reasonable as well as their description are summarised in Table 5.

Taken together, we recommend the YGTSS-R to measure tic severity [141]. Alternatively, the following instruments may be used: Shapiro Tourette-Syndrome Severity Scale (STSS) [151], the Tourette's Syndrome Clinical Global Impression Scale (TS-CGI) [151] and the Tourette Disorder Scale (TODS) [152].

Assessment of quality of life in TS

In children and in adults, it is paramount not only to assess the degree of impairment, but also the overall quality of life. Loss of quality of life entails that the disorder is time consuming, causes significant distress and interferes with major domains of daily life, such as school, work status and (social) relationships. Quality of life can be reliably measured with various instruments. We recommend the TS-specific quality of life scales [for adults: the Gilles de la Tourette Quality of Life Scale (GTS-QOL) and its equivalent used in paediatric population: the Gilles de la Tourette Syndrome-Quality of Life Scale for children and adolescents (C&A-GTS-QOL)] [146, 170]. Storch et al. [125, 126] developed another scale to measure functional impairment in group of children with tics, the Mini-Child Tourette Syndrome Impairment Scale. Also more general quality of life scales can be implemented, including for example the Short Form Health Survey [36-item from (SF-36) or 12-item version (SF-12)] and Euro-Qol-5 Dimension [171, 172] which are validated in general and psychiatric populations. An overview and suggestions are given in Tables 4 and 5.

Assessment of comorbidities

ADHD

A clinical interview supplemented with objective self-administrative and clinically-guided ADHD questionnaires is the most commonly used assessment for diagnosing ADHD in children and adults. In children, parents/caregivers and schoolteachers are the main providers of information about psychosocial factors, with standardised measures used to assess ADHD symptoms and functional impairment compared to children of a similar age. The particular challenge in assessment of adults lies in the gathering of reliable information on behaviour that has started before age 12 to

Table 4 Impairment assessments in children and adults with tics

Scale	Clinical usefulness	Age Group recommended	Rater	Range of scores	Time (min)
Impairment measured with the Yale Global Tic Severity Scale (YGTSS) [141]	Separately rates impairment due to motor or vocal tics	Adults and children	Health professional and the patient	0–50 (0 is the best score)	Max. 5
Global Assessment of Functioning (C-GAS) [166]	Axis five of DSM-IV TR (2002 [1]) and DSM-5, functioning in all areas of development, school/work and psychosocial functioning	Adults and children	Health professional and the patient	0–90 (90 is the best score)	Max. 10
Clinical Global Severity Scale (CGI-S) [145]	Assesses change in global daily functioning	Adults and children	Health professional	0 = much deteriorated and, via 3 = no change, to 6 = very much improved	Max. 5
The Gilles de la Tourette Syndrome-Quality of Life Scale GTS-QOL [167]	27 item scale is based on the health-related quality of life scale (HR-QOL), contains four domains: psychological problems, cognitive problems, physical/activity of daily living problems and obsessive–compulsive themes	Adults	Self-rating	Response ranges between 0 and 4, range 0–100 (0 is the best score)	Max. 30
The Gilles de la Tourette Syndrome-Quality of Life Scale for Children and Adolescents (C&A-GTS-QOL) [146]	A 27-item scale consisting of 4 subscales (psychological, physical, obsessive–compulsive and cognitive)	Children	Two age-adjusted versions: (1) an interview to be administered by a qualified clinician for children aged 6–12 years and (2) a self-report questionnaire for adolescents aged 13–18 years	Response ranges between 0 and 4, range 0–100 (0 is the best score)	Max. 30
The Mini Child Tourette's Syndrome Impairment Scale (CTIM) [126]	37-item parent rated instrument covering school, home, and social activities that may be impaired by tics or comorbid problems (including OCD symptoms, depression, anxiety, oppositional/disruptive behaviour, hyperactivity, and inattention)	Children	Parent also self-evaluation and short version are available [168, 169]	Each item is rated as: not at all (0), just a little (1), pretty much (2), or very much (3) problematic for the child due to tics or non-tic symptoms. Range 0–111 separately for tics and non-tics (0 is the best score)	Max. 30

Table 5 Scales "recommended", "suggested" and "reasonable" for evaluation of tics, premonitory urges, impairment and psychiatric comorbidities. Results are based on the ESSTS Survey and recommendations by Martino et al. [151]

Domain of assessment	Scale	Recommendation (in clinical practice or research)
Tics	YGTSS	Recommended
	PTQ/ATQ	Suggested
	TSSL	Suggested
	STSS	Reasonable
	TS-CGI	Reasonable
	CGI-S	Reasonable
	TODS	Reasonable
	RVBTRS	Reasonable
	TSGS	Reasonable
	GTRS	Reasonable
	MOVES rater	Reasonable
	MOVES patient	Reasonable
	PRQPT	Reasonable
	Apter 4-q	Reasonable
Tics and comorbidities	A-TAC	Reasonable
Premonitory urges	PUTS	Recommended
Impairment	Impairment in YGTSS	Recommended
	GTS-QOL	Recommended
	C&A-GTS-QOL	Recommended
	CTIM	Suggested
	C-GAS	Suggested
OCD	Y-BOCS	Recommended
	CY-BOCS	Recommended
ADHD	SNAP	Recommended
	CAARS	Recommended
	WURS	Suggested
	Qb + ©	Reasonable

YGTSS the Yale Global Tic Severity Scale, *STSS* Shapiro Tourette-Syndrome Severity Scale, *TS-CGI* Tourette Syndrome-Clinical Global Impression, *TODS* the Tourette's Disorder Scale, *PUTS* Premonitory Urge for Tics Scale, *RVBTRS* Rush Video-Based Tic Rating Scale, *TSGS* Tourette Syndrome Global Scale, *GTRS* Global Tic Rating Scale, *MOVES* Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey, *PTQ* Parent Tic Questionnaire, *ATQ* Adult Tic Questionnaire, *TSSL* Tourette Syndrome Symptom List, *A-TAC* Autism–Tics, ADHD, and other Co-morbidities inventory, *PRQPT* Proxy Report Questionnaire for Parents and Teachers, *Apter 4-q* Apter 4-questions screening, *GTS-QOL* The Gilles de la Tourette Syndrome-Quality of Life Scale, *C&A-GTS-QOL* Gilles de la Tourette Syndrome-Quality of Life Scale in children and adolescents, *CTIM* Child Tourette's Syndrome Impairment Scale, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale, *SNAP* Swanson, Nolan and Pelham questionnaire, *CAARS* Children's version of the Connors ADHD Rating Scale, *WURS* the Wender Utah Rating Scale, *Qb + ©* Quantified Behaviour Test Plus, *C-GAS* The Children's Global Assessment Scale, *CGI-S* The Clinical Global Impression—Severity scale, *ADHD* attention deficit hyperactivity disorder, *OCD* obsessive–compulsive disorder

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.

According to the ESSTS survey, most experts use a combination of both clinical interview and scales to diagnose ADHD, most commonly: Swanson, Nolan and Pelham questionnaire (SNAP) [136], Children's or adults' versions of the Connors ADHD Rating Scale (CAARS), the Conners Comprehensive Behaviour Rating Scale (CBRS) [173] and the Wender Utah Rating Scale (WURS) [150]. For summary of available scales as well as recommendations please consult Table 3 and previous version of the guidelines [4].

Other comorbidities: OCD, anxiety, mood, rage attacks

Assessment of other comorbidities is generally performed using clinical interview supplemented with rating scales, both in diagnosing and differential diagnosis, evaluation of treatment and in the context of clinical trials, as reported by the majority of experts in the ESSTS survey. Assessment scales useful in evaluation of these symptoms in children and adults are summarised in Table 3 and our recommendations are shown in Table 5.

The most widely investigated, used and therefore recommended scale is the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) and its equivalent used for children: the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and its revised version the CY-BOCS-II [133].

Since rage attacks have been identified as a common and disabling symptom not only in children, but also in adults, just recently, a new tool has been developed to specifically asses rage attacks in adults with TS, the RAQ-R [73].

Assessment of neuropsychological functioning

Contrary to assumptions, it is unlikely that cognitive difficulties solely result from chronic tics and are often associated with co-existing conditions, particularly attentional problems or ADHD and likely also OCD [79, 92], with some evidence for inherent executive function problems (especially inhibition control) in TS [87]. Therefore, only in selected cases, in which patients present with cognitive complaints (such as attention or memory problems), learning/school problems or daily life problems, and particularly in those with comorbid conditions, formal neuropsychological testing is recommended, which may help guide intervention and give recommendations how to support the child at school

Table 6 Suggested neurocognitive assessments for use in children and adults with TS

Neuropsychological domains	Children	Adults
Intellectual function	WPPSI–IV WISC-V	WAIS-IV
Attention		
Sustained attention	CPT	CPT
Selective attention	TEA-Ch–II	TAP
Working memory auditory/spatial	Digit span, Corsi blocks	Digit span, Corsi blocks, WMS-IV
Executive functions–cognitive aspects		
Conceptual elaboration/categorization	D-KEFS	D-KEFS
Planning	BADS-C	BADS
Flexibility	Rey CFT	Rey CFT
Inhibition	Stroop GNG Wisconsin CST Trail making A,B	Wisconsin CST Stroop GNG Trail making A,B
Executive functions–behavioural/emotional aspects		
Behavioural inhibition	BRIEF–2	BRIEF-A
Emotional regulation	BADS-C	BADS
Social cognition	Facial expression recognition	Faux-pas test, facial expression recognition, FEEST, SEA
Memory	RVDLT, AVLT	MEM-IV
Visual spatial skills	Benton Test	VOSP, BJLO
Literacy and numeracy	WIAT-III	BDAE (BNT) & CAB-DC
Motor skills and coordination	VMI–6	PP

AVLT Auditory Verbal Learning Test [174], *BADS* Behavioural Assessment of the Dysexecutive Syndrome [175], *BADS-C* Behavioural Assessment of the Dysexecutive Syndrome for Children [175], *BDAE* Boston Diagnostic Aphasia Examination [176], *BJLO* Benton Judgement of Line Orientation [177], *BNT* Boston Naming Test [178], *BRIEF-2* Behaviour Rating Inventory of Executive Function-Second edition [179], *BRIEF-A* Behaviour Rating Inventory of Executive Function for Adults [180], *CAB-DC* Cognitive Assessment Battery for Dyscalculia, *CPT-III* Continuous Performance Test-Connors Third Edition [181], *D-KEFS* Delis Kaplan Executive Function System [182], *FEEST* Facial Expression of Emotions [183], *GNG* Go no go task [184], *PP* Purdue Pegboard [185], *RVDLT* Rey Visual Design Learning Test [186], *Rey CFT* Rey complex Figure Test [187], *TEA-ch*-2 Test of Everyday Attention in Children-Second edition [188], *TAP* Test of Attentional Performance [188], *VOSP* Visual Object and Space Perception [189], *VMI-6* Beery Buktenika Test of Visual Motor Integration-Sixth edition [190], *WAIS-IV* Wechsler Adult Intelligence Scale-Fourth Edition [191], *Wisconsin CST* Wisconsin Card Sorting Test [192], *WIAT-III* Wechsler Individual Achievement Test-third edition [193], *WPPSI-4* Wechsler Preschool and Primary Scale of Intelligence-Fourth edition [194], *WISC-V* Wechsler Intelligence Scale for Children-Fifth Edition [195], *WMS-IV* Wechsler Memory Scale [196], *SEA* Social Cognition and Emotional Assessment

and the adult in their everyday professional or vocational life. Given the wide difference in accessing experienced neuropsychologists across centres around the world, specific neuropsychological batteries are not advocated, but in Table 6 we summarise well-known and commonly used measures.

Conclusions

TS represents a wide range of tics and co-existing symptoms with a varied and heterogeneous presentation. In this updated guideline, we recommend clinically useful 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 is sufficient to guide diagnosis and treatment. However, psychiatric comorbidities occur in more than three quarters of patients that may require referral for specialised care. Further, in a minority of cases a more extensive neurological and psychiatric screen is necessary to differentiate tics from other hyperkinetic or psychiatric disorders including functional "tic-like" movements. Finally, neuropsychological assessment can be useful to identify specific learning and cognitive impairments to aid academic progress and reasonable adjustments in life.

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REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part II: psychological interventions

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Abstract
Part II of the European clinical guidelines for Tourette syndrome and other tic disorders (ECAP journal, 2011) provides updated information and recommendations for psychological interventions for individuals with tic disorders, created by a working group of the European Society for the Study of Tourette Syndrome (ESSTS). A systematic literature search was conducted to obtain original studies of psychological interventions for tic disorders, published since the initial European clinical guidelines were issued. Relevant studies were identified using computerized searches of the MEDLINE and PsycINFO databases for the years 2011–2019 and a manual search for the years 2019–2021. Based on clinical consensus, psychoeducation is recommended as an initial intervention regardless of symptom severity. According to a systematic literature search, most evidence was found for *Habit Reversal Training* (HRT), primarily the expanded package *Comprehensive Behavioral Intervention for Tics* (CBIT). Evidence was also found for *Exposure and Response Prevention* (ERP), but to a lesser degree of certainty than HRT/CBIT due to fewer studies. Currently, cognitive interventions and third-wave interventions are not recommended as stand-alone treatments for tic disorders. Several novel treatment delivery formats are currently being evaluated, of which videoconference delivery of HRT/CBIT has the most evidence to date. To summarize, when psychoeducation alone is insufficient, both HRT/CBIT and ERP are recommended as first-line interventions for tic disorders. As part of the development of the clinical guidelines, a survey is reported from ESSTS members and other tic disorder experts on preference, use and availability of psychological interventions for tic disorders.

Keywords Tourette syndrome · Tic disorders · Treatment guidelines · Behavior therapy · Comprehensive behavioral intervention for tics · Habit reversal training · Exposure and response prevention

Introduction

Tic disorders are neurodevelopmental disorders characterized by recurrent motor and/or vocal tics. Tics can be transient, as represented by the diagnosis Provisional Tic Disorder in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1, 2], or they can persist for over a year as a chronic condition, described in the DSM-5 as Tourette's Disorder (from now on referred to as Tourette syndrome [TS]) and Persistent (Chronic) Motor or Vocal Tic Disorder [CTD]. Typically, tics have an onset between 4 and 6 years of age, are at their worst between 10 and 12 years, and decrease naturally during adolescence and early adulthood [3]. Psychiatric comorbidities are common among individuals with TS/CTD and tend to persist through the life course [4]. For patients who seek TS/CTD-specific treatment, psychological and medical interventions are available.

All parts of the European clinical guidelines for TS and other tic disorders have been created by a working group of the European Society for the Study of Tourette Syndrome (ESSTS). The initial European clinical guidelines were

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published in 2011 and provided diagnostic and treatment recommendations based on a literature search of clinical trials and case studies up to that point [5, 6]. The current paper is an updated version of part III (now referred to as part II) of these guidelines, focusing on new clinical trials of psychological interventions for tic disorders published after 2011. In addition, early evidence of newly developed psychological interventions for tic disorders are described, including different modalities of treatment delivery, third-wave interventions, as well as overall future directions. Furthermore, results from a survey among ESSTS members and tic disorder experts on preference, use and availability of psychological interventions is reported on. The term TS is used throughout these guidelines for both TS, CTD and Provisional Tic Disorder. Only if there are substantial differences between the tic disorders, a more specific term is used.

Method

For the current update of part II of the European clinical guidelines, a literature search was performed. The aim was to identify relevant research on the efficacy and effectiveness of psychological interventions for TS, as well as adaptations of interventions when comorbid psychiatric conditions are present, published between January 2011 and June 2019. The databases MEDLINE and PsycINFO at Ovid were searched using relevant MeSH terms. Details on our search strategy can be found in Online Resource 1. In addition, the reference lists of the (review) articles identified through MEDLINE and PsycINFO were reviewed for additional studies. In addition to the studies identified through systematic review, to make the publication list as comprehensive as possible, studies were also added by the authors (i.e. through precedent knowledge about relevant publications). Shortly prior to publication, we updated the literature search to also include studies between June 2019 and May 2021. The methodology of the ESSTS survey is presented in an editorial in the current issue of this journal.

Results

Evidence-based psychological interventions

In the 2011 European clinical guidelines, behavior therapy (BT) was recommended as a first-line intervention for tic disorders in children and adults [5, 6]. The rationale for using BT for treating tic disorders is based on the fact that tics can be suppressed for various lengths of time, and that the expression of tics, beyond their neurobiological origin, is influenced by contextual factors. These contextual factors include the perception of premonitory urges and other internal (e.g. emotional) states and environmental contingencies (e.g. specific situations or activities, stress-inducers, social reactions). The goal of BT is to provide patients with tic-specific behavioral techniques to enhance self-control and to decrease factors that worsen or maintain tics.

Of the different BT interventions available, most experimental evidence was found for *Comprehensive Behavioral Intervention for Tics* (CBIT), where *Habit Reversal Training* (HRT) is considered the main component [7, 8]. Evidence was also found for *Exposure and Response Prevention* (ERP) [9]. The 2011 European clinical guidelines recommended both HRT/CBIT and ERP as first-line interventions. In 2012, Canadian clinical guidelines were published, which also recommended BT as a first-line intervention for tic disorders, stating that especially CBIT is supported by strong evidence for efficacy and safety [10]. Recently, the American Academy of Neurology (AAN) published their clinical guidelines for the treatment of tic disorders, again recommending BT as a first-line intervention for tic disorders. The AAN guidelines specify that clinicians should offer CBIT as an initial treatment option prior to other psychological interventions and to pharmacotherapy (PT). If CBIT is unavailable, ERP may be an acceptable alternative. According to the AAN guidelines, CBIT is the only intervention to achieve the highest rating ("high confidence" to reduce tics compared to the control condition), which was not achieved by any of the PTs [11].

The following sections describe clinical trials of psychological interventions, published since the 2011 European clinical guidelines, based on our current literature search. Table 1 presents details on randomized controlled trials (RCTs) published since 2011, as well as influential RCTs published prior to 2011. Treatments for tic disorders that were mentioned in the 2011 European clinical guidelines, but were not examined or supported by RCTs (such as *massed negative practice*, *self-monitoring and relaxation training*), and where no new substantial evidence has been published since are not covered in this update [5].

Psychoeducation

Psychoeducation refers to the clear sharing of understandable, up-to-date information about the symptoms, cause, prognosis, potential management, treatment and daily experience of a condition. Such information is typically included as a first step in various treatment protocols of evidence-based psychological interventions for tic disorders (e.g. [12, 13]). However, as a stand-alone intervention aimed at reducing tic severity, psychoeducation (sometimes also extended with information on healthy habits and common comorbid conditions, and referred to as *psychoeducation and supportive psychotherapy* [PST]) has been shown inferior to BT and

Table 1 Randomized controlled trials of psychological interventions for tic disorders published since 2011, as well as a selection* of previous influential trials to enable comparison

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Verdellen et al. (2004) [9]	HRT vs ERP	*N* = 43 Age 7–55	**YGTSS-TTS**: HRT: 24.1 (pre) to 19.7 (post) Within-group effect size: 1.06 ERP: 26.2 (pre) to 17.6 (post) Within-group effect size: 1.42	**3FU**: *YGTSS-TTS*: HRT: 13.5 ERP: 14.0	**Duration**: HRT: 10 sessions (1 h, weekly); ERP: 12 sessions (2 h, weekly) **Results**: No significant between-group effect on the YGTSS-TTS. Significant within-group effects on the YGTSS-TTS for each group **Follow-up**: Treatment effect maintained for both groups **Limitations**: Uncertain whether the study was powered to detect significant between-group effects. 3FU included 25 participants who had been crossed over to the other group
Piacentini et al. (2010) [8]	CBIT vs PST	*N* = 126 Age 9–17	**YGTSS-TTS**: CBIT: 24.7 (pre) to 17.1 (post) PST: 24.6 (pre) to 21.1 (post) Between-group effect size: 0.68	**6FU**: CBIT: 20 out of 23 available initial treatment responders were still classified as treatment responders (according to the CGI-I)	**Duration**: 8 sessions (during 10 weeks; first two sessions 1.5 h, remaining sessions 1 h). 3 monthly booster sessions for responders **Interventions**: CBIT included psychoeducation about tic disorders, HRT, relaxation training, and functional analysis; PST included psychoeducation and supportive psychotherapy **Results**: Significant between-group effect on the YGTSS-TTS (in favor of CBIT) **Follow-up**: Treatment effects were maintained **Limitations**: Follow-up data were only available for initial treatment responders

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Himle et al. (2012) [54]	F2F CBIT vs VC CBIT	*N* = 20 Age 8–17	**YGTSS-TTS**: F2F CBIT: 24.1 (pre) to 17.6 (post) VC CBIT: 23.4 (pre) to 15.6 (post)	**4FU**: *YGTSS-TTS:* F2F CBIT: 20.1 VC CBIT: 16.8	**Duration**: 8 sessions (weekly) via a VC software **Interventions**: CBIT included psychoeducation about tic disorders, HRT, relaxation training, and functional analysis **Results**: No significant between-group effect on the YGTSS-TTS. Significant within-group effects on the YGTSS-TTS for each group **Follow-up**: Significant within-group effect from pre to 4FU for the combined sample **Limitations**: Uncertain whether the study was powered to detect significant between-group effects
Wilhelm et al. (2012) [15]	CBIT vs PST	*N* = 122 Age 16–69	**YGTSS-TTS**: CBIT: 24.0 (pre) to 17.8 (post) PST: 21.8 (pre) to 19.3 (post) Between-group effect size: 0.57	**6FU**: CBIT: 12 out of 15 available initial treatment responders were still classified as treatment responders (according to the CGI-I)	**Duration**: 8 sessions (during 10 weeks; first two sessions 1.5 h, remaining sessions 1 h). 3 monthly booster sessions for responders **Interventions**: CBIT included psychoeducation about tic disorders, HRT, relaxation training, and functional analysis; PST included psychoeducation and supportive psychotherapy **Results**: Significant between-group effect on the YGTSS-TTS (in favor of CBIT). Significantly higher proportion of treatment responders in the CBIT group (24 vs. 4), as measured by the CGI-I **Follow-up**: Treatment effects were maintained **Limitations**: Follow-up data were only available for initial treatment responders

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
McGuire et al. (2015) [22]	LWT vs Waitlist	*N* = 24 Pediatric sample	**YGTSS-TTS**: LWT: 20.2 (pre) to 14.3 (post) Waitlist: 24.7 (pre) to 24.8 (post) **YGTSS Impairment Score**: LWT: 27.5 (pre) to 8.3 (post) Waitlist: 31.7 (pre) to 23.8 (post) Between-group effect size: 1.50	**1FU**: 1FU was completed for 5 out of 10 initial treatment responders (according to the CGI-I). No change was found between the post and 1FU YGTSS Impairment scores, indicating maintenance of the treatment effects	**Duration**: 10 sessions (weekly) **Interventions**: LWT included abbreviated HRT, cognitive restructuring, problem solving, parent training, emotion regulation, overcoming tic-related avoidance, talking about tics with peers and coping at school, and improving self-esteem **Results**: Significant between-group effect on the YGTSS Impairment score (primary outcome) (in favor of LWT). No significant between-group effect on the YGTSS-TTS, but significant within-group effect for the LWT group on the same measure **Follow-up**: Treatment effects were maintained **Limitations**: Follow-up data were only available for initial treatment responders
Ricketts et al. (2016) [55]	VC CBIT vs Waitlist	*N* = 20 Age 8–16	**YGTSS-TTS**: VC CBIT: 25.8 (pre) to 18.5 (post) Waitlist: 22.0 (pre) to 20.3 (post) Between-group effect size: 0.15 (partial η^2)	**FU**: N/a	**Duration**: 8 sessions (during 10 weeks; first two sessions 1.5 h, remaining sessions 1 h) via a VC software **Interventions**: CBIT included psychoeducation about tic disorders, HRT, relaxation training, and functional analysis **Results**: Significant between-group effect on the YGTSS-TTS (in favor of VC CBIT)
Yates et al. (2016) [49]; Dabrowski et al. (2018) [50]	Group HRT vs Group PE	*N* = 33 Age 9–13	**YGTSS-TTS**: N/a **YGTSS-MTSS**: Group HRT: 17.7 (pre) to 15.1 (post) Group PE: 16.3 (pre) to 15.9 (post) Between-group effect size: 0.55	**12FU**: *YGTSS-MTSS:* Group HRT: 12.2 Group PE: 13.8	**Duration**: 8 sessions (first two sessions 1.5 h, remaining sessions 1 h) delivered in a group format **Results**: Significant between-group effect on the YGTSS-MTSS (in favor of Group HRT) **Follow-up**: Both groups combined improved significantly on the YGTSS-TTS and the YGTSS-MTSS between pre and 12FU **Limitations**: YGTSS-TTS were not reported at pre and post

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Seragni et al. (2018) [19]	HRT vs UC	*N* = 21 Pediatric sample	**YGTSS-TTS**: N/a	**3FU**: *YGTSS-MTSS:* Significant within-group effect for HRT and UC combined into one group. Scores n/a	**Duration**: HRT: 8 sessions (during 10 weeks); UC: 3 sessions (during 10 weeks) **Results**: No significant between-group effect on any reported YGTSS score **Follow-up**: Significant within-group effect for HRT and UC combined into one group **Limitations**: High number of dropouts, only 13 participants completed the trial. Uncertain whether the study was powered to detect significant between-group effects. Effect sizes were not reported
Rizzo et al. (2018) [14]	BT vs. PE PT vs. PE BT vs. PT	*N* = 110 Age 8–17	**YGTSS-TTS**: BT: 19.8 (pre) to 11.4 (post) PT: 24.1 (pre) to 15.7 (post) PE: 22.0 (pre) to 21.7 (post)	**FU**: *YGTSS-TTS at 3 months post BT/PE and 5 months post initiation of PT:* BT: 12.4 PT: 14.7 PE: 20.7	**Duration**: 8 sessions (weekly, first two sessions 1.5 h, remaining sessions 1 h) **Interventions**: BT included HRT or ERP; PT included risperidone, aripiprazole or pimozide **Results**: Significant between-group effects on the YGTSS-TTS for BT vs. PE and PT vs. PE (in favor of BT and PT) **Limitations**: Uncertain whether the study was powered to detect significant between-group effects between BT and PT. Effect sizes were not reported
Andrén et al. (2019) [59]	Internet ERP vs. Internet HRT	*N* = 23 Age 8–16	**YGTSS-TTS**: Internet ERP: 23.8 (pre) to 18.3 (3FU) Within-group effect size: 1.12 Internet HRT: 23.5 (pre) to 20.2 (3FU) Within-group effect size: 0.50	**12FU**: *YGTSS-TTS:* Internet ERP: 16.9 Internet HRT: 19.4	**Duration**: 10 weeks of therapist-supported (via text messages) internet-delivered treatment **Interventions**: In addition to the ERP or HRT core elements, both groups included functional analysis and parent training **Design**: Study did not aim to compare groups **Results**: Significant within-group effect on the YGTSS-TTS for the Internet ERP group, but not the Internet HRT group **Follow-up**: Effects were maintained at 12FU

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Nissen et al. (2019, 2021) [43, 52]	Individual HRT + ERP vs Group HRT + ERP	*N* = 59 Age 9–17	**YGTSS-TTS**: Individual HRT + ERP: 23.8 (pre) to 14.3 (post) Within-group effect size: 1.21 Group HRT + ERP: 23.4 (pre) to 15.9 (post) Within-group effect size: 1.38	**12FU**: *YGTSS-TTS:* Individual HRT + ERP: 12.7 Group HRT + ERP: 12.8	**Duration**: 8 regular sessions and 1 booster session, delivered individually or in a group format **Results**: No significant between-group effect on the YGTSS-TTS. Significant within-group effects on the YGTSS-TTS for each group **Follow-up**: Treatment effects were maintained for both groups at 12FU **Limitations**: Uncertain whether the study was powered to detect significant between-group effects
Chen et al. (2020) [63]	CBIT + UC vs. UC	*N* = 46 Age 6–18	**YGTSS-TTS**: CBIT: 19.3 (pre) to 10.4 (post) UC: 17.7 (pre) to 14.5 (post) Between-group effect size: 0.56	**3FU**: *YGTSS-TTS:* CBIT: 6.6	**Duration**: CBIT: 4 sessions (during 3 months) **Interventions**: CBIT included psychoeducation, habit reversal training, relaxation training, and relapse prevention; UC included psychoeducation and 50 mg of pyridoxine (per day) **Results**: Significant between-group effect on the YGTSS-TTS (in favor of CBIT + UC) **Follow-up**: Further improvement for the CBIT + UC-group in a within-group analysis at 3FU **Limitations**: No intention-to-treat analysis
McGuire et al. (2020) [33]	HRT + DCS vs. HRT + placebo	*N* = 20 Age 8–17	**YGTSS-TTS**: N/a	**FU**: N/a	**Duration**: HRT: 1 session **Interventions**: HRT; 50 mg of DCS or placebo. DCS was hypothesized to enhance the effect of HRT **Results**: Significant between-group effect on the Hopkins Motor/Vocal Tic Scale (in favor of HRT + DCS), for the two bothersome tics targeted in treatment **Limitations**: Did not use the YGTSS. Low dose of HRT compared to previous trials (only 1 session)

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Rachamim et al. (2020) [60]	Internet CBIT vs. Waitlist	*N* = 41 Age 7–18	**YGTSS-TTS**: Internet CBIT: 22.7 (pre) to 16.1 (post) Waitlist: 21.9 (pre) to 20.9 (post) Between-group effect size: 0.20 (partial η^2)	**6FU**: *YGTSS-TTS:* Internet CBIT: 11.0	**Duration**: 9 weeks of therapist-supported (via telephone) internet-delivered treatment + 6 monthly booster sessions **Results**: Significant between-group effect on the YGTSS-TTS (in favor of Internet CBIT) **Follow-up**: Large within-group effect for the Internet CBIT group at 6FU
Singer et al. (2020) [56]	DVD HRT vs. HRT	*N* = 44 Age 7–13	**YGTSS-TTS**: DVD HRT: 27.8 (pre) to 18.8 (post) HRT: 28.2 (pre) to 20.7 (post)	**FU**: N/a	**Duration**: HRT: 8 sessions (during 10 weeks) **Interventions**: DVD HRT-group received a DVD and written instructions on how to use HRT at home with the support of a parent; HRT-group received regular face-to-face HRT **Results**: No significant between-group effect. Significant within-group effects in both groups **Limitations**: Uncertain whether the study was powered to detect significant between-group effects. Large dropout rates and the lack of an intention-to-treat analysis make results difficult to interpret

Table 1 (continued)

Study	Groups	Subjects	Efficacy	Follow-up	Comments
Zimmerman-Brenner et al. (2021) [51]	Group CBIT vs. Group PE	*N* = 61 Age 8–15	**YGTSS-TTS**: Group CBIT: 24.8 (pre) to 39.8 (post) Group PE: 22.0 (pre) to 37.1 (post)	**3FU**: *YGTSS-TTS:* Group CBIT: 18.4 Group PE: 21.8	**Duration**: 8 weekly sessions (first two sessions 1.5 h, remaining sessions 1 h; considered the acute treatment phase) + 3 monthly 1-h booster sessions (during the follow-up phase). All sessions were delivered in a group format **Results**: No significant between-group effect. Significantly increased YGTSS-TTS in both groups (within-group analysis) at post-treatment, seemingly driven by increased vocal tic severity **Follow-up**: Significantly decreased YGTSS-TTS in both groups (within-group analysis) when comparing baseline to the 3-month follow-up **Limitations**: Uncertain whether the study was powered to detect significant between-group effects. No intention-to-treat analysis

*The previous trials were selected following expert consensus as especially important for the recommendations of the initial European clinical guidelines published in 2011

1–3–4–6–12FU 1–3-4–6-12 months post-treatment time-point follow-up; *BT* behavior therapy; *CBIT* comprehensive behavioral intervention for tics; *CGI–I* Clinical Global Impressions—Improvement scale; *CTD* chronic tic disorder; *DCS* D-cycloserine; *ERP* exposure and response prevention; *F2F* face-to-face; *FU* follow-up; *HRT* habit reversal training; *LWT* Living with tics; *N/a* not available; *PE* psychoeducation; *post* post-treatment time-point; *pre* pre-treatment/baseline time-point; *PST* psychoeducation and supportive psychotherapy; *PT* pharmacotherapy; *TS* Tourette syndrome; *UC* usual care; *VC* videoconference; *YGTSS* Yale Global Tic Severity Scale; *YGTSS–MTSS* Yale Global Tic Severity Scale—Motor Tic Severity Score; *YGTSS–TTS* Yale Global Tic Severity Scale—Total Tic Severity Score

PT in several RCTs [8, 14, 15]. In a review of psychoeducation for teachers and peers, it was concluded that psychoeducation increases knowledge, positive attitudes and behaviors towards individuals with TS [16].

Despite psychoeducation being described in clinical guidelines as a first important step of any treatment for TS [5, 11], evidence on what specific elements should be addressed is lacking. A comprehensive overview of suggested information to include can be found in a review by Wu and McGuire [17].

Habit reversal training (HRT) and Comprehensive behavioral intervention for tics (CBIT)

HRT consists of two primary parts: First, awareness training, which includes different techniques to increase awareness of tic expression and associated premonitory urges. Second, competing response training, in which physically incompatible responses are identified and applied, which prevent tics from being expressed. In HRT, tics are treated on a one-by-one basis. All current tics are listed and rated in terms of their severity. Typically, the most bothersome tic from this hierarchy is selected to be treated first. This tic is then subjected to awareness training, in which the patient learns to detect when the tic is occurring, as well as the signals that precede tic. Once a patient has developed a good awareness of the tic and can predict the occurrence of the tic, competing response training begins. Competing response training involves the selection and subsequent implementation of a physically incompatible behavior designed to prevent tics from occurring. The competing response generally employs the same muscles as the tic and should be able to be performed for a sustained period. Once a competing response has been practiced in a session, the patient continues to practice it at home. As soon as the patient learns to use the competing response to reliably prevent the tic, the treatment focus is shifted to the next tic in the hierarchy [12, 18]. CBIT is an expanded version of HRT, and additionally includes therapeutic strategies such as relaxation training, contingency management, and interventions based on functional analyses to address contextual factors which influence tic expression [8, 12].

The 2011 European clinical guidelines reported several RCTs of HRT/CBIT, demonstrating medium to large treatment effects. The largest RCT evaluated CBIT in 126 children (9–17 years) with TS or CTD [8]. In this study, CBIT was superior to psychoeducation and PST in reducing tic severity (as measured by the Yale Global Tic Severity Scale - Total Tic Severity Score [YGTSS-TTS]; effect size: 0.68, as compared to PST). In a 6-month follow-up of treatment responders (defined as a score <3 on the Clinical Global Impressions–Improvement Scale [CGI-I]) of both groups, treatment gains were shown to be maintained for the majority of the responders in a completer analysis. In parallel to this trial, Wilhelm et al. [15] published an RCT in 2012 comparing CBIT with PST in 122 adults (16–69 years) with TS or CTD. In line with the pediatric trial, all patients received eight sessions of either condition, while responders additionally received three monthly booster sessions. As in the pediatric trial [8], CBIT was found to be superior to PST (effect size: 0.57). The responder rate (defined as CGI-I <3) was, however, lower in the adult trial (38.1% compared to 52.5% in the pediatric trial), which was hypothesized to reflect that the adult participants suffered from a more treatment-resistant form of the disorder. The overall dropout rate was 13.9%, with no difference between groups. Treatment responders of both groups continued to show benefits up to the 6-month follow-up, in a completer analysis.

The literature search also identified a few smaller clinical trials of HRT. Seragni et al. conducted a randomized pilot study (N=21) comparing HRT with a control condition (three sessions of routine treatment with a neuropsychiatrist, without prescription of PT) for young people with TS [19]. Participants showed an improvement in tic reduction and global functioning in both groups, without significant between-group differences. Interpretation of the results was hampered by the small sample size and a high number of dropouts in both groups. Viefhaus et al. examined the efficacy of a German BT program (similar to CBIT) including HRT, psychoeducation and additional behavioral interventions (e.g. functional interventions) for young people (8–16 years; N=27) with TS/CTD [20]. In a within-group design (8 weeks pre-treatment; 16 sessions treatment), significant improvements were found on tic severity (YGTSS-TTS, within-group effect size: 0.89) and tic-related impairment (YGTSS Impairment Score, within-group effect size: 0.31) at post-treatment. Bennett et al. evaluated a modified version of CBIT for use among very young patients (5–8 years) in an open study [21]. Compared to the previously published CBIT protocol [12], the adaptations included fewer sessions (six instead of eight), larger parent involvement, and a simplified explanation of HRT through playing cards picturing body movements and competing responses. The results showed a medium-sized, significant within-group effect (d=0.73) on the YGTSS-TTS at post-treatment, which later was maintained at a 12-month follow-up. The study provides preliminary evidence for CBIT also being efficacious in this younger patient group.

Further adaptations to BT have been made to broaden the focus from reducing tic severity to improving the individual's overall quality of life. McGuire et al. evaluated a modular treatment protocol ("Living with Tics"; LWT) that incorporates HRT with psychoeducation, problem-solving, distress tolerance, and coping at school, with the aim of improving resilience and reducing tic-related impairment [22]. Preliminary findings of this intervention

in youth (N=24) showed the LWT intervention to be efficacious in improving quality of life relative to a waitlist control (YGTSS Impairment Score, effect size: 1.50). Ten participants (83%) in the LWT condition were rated as treatment responders, compared to four participants (33%) in the waitlist condition. Treatment gains were maintained at a 1-month follow-up [22].

To summarize, several RCTs support the use of HRT/CBIT as an effective treatment for tics in children and adults with TS.

Exposure and response prevention (ERP)

Similar to HRT, ERP is based on learning theory. In ERP, the individual practices suppressing tics for prolonged periods of time (response prevention), with gradually increased exposure to premonitory urges and environmental factors (e.g. situations and activities) that are likely to induce tics, with the aim to increase urge tolerance and thereby reduce tics. Unlike HRT, no tic hierarchy needs to be created and all tics are worked with at the same time. In ERP, the patient is first trained to enhance tic suppression. A stopwatch is used to record tic suppression times and the patient is motivated to beat his/her record on each new trial. In the next phase, exposure is optimized by focussing on the premonitory urges, being exposed to stimuli that are known to elicit tics and practicing in various situations and activities. Meanwhile, the patient is instructed to keep resisting all tics. Apart from the in-session training, the patient is encouranged to continue practicing ERP on his/her own between the sessions [9, 23].

In the 2011 European clinical guidelines part III on behavioral interventions one RCT of ERP for the treatment of tic disorders was reported [9], where 43 children and adults (7–55 years) were randomized to either ERP or HRT. The results demonstrated comparable effects for both treatments (within-group effect sizes: 1.42 for ERP and 1.06 for HRT). Results were maintained up to a 3-month follow-up, but the interpretation is hampered by cross over between treatments. Since 2011, only open studies have been published examining the treatment effects of ERP. In a naturalistic study by Andrén et al. [24], 74 participants (6–17 years) received BT at a TS specialist clinic in Sweden. Out of the 74 participants, 46 received ERP, 14 received HRT, and 14 received various combinations of the two. Results showed a significant and large within-group effect (d=1.03) on the YGTSS-TTS for the combined BT group at post-treatment, with further improvement at a 12-month follow-up. The study provides some additional open data on the efficacy of mainly ERP, but primarily the authors conclude that BT can be delivered in a naturalistic specialist clinical setting, with comparable effects to RCTs.

Cognitive interventions

To date, there are no RCT data supporting cognitive interventions as a stand-alone treatment for TS. Since the 2011 European clinical guidelines, a new treatment model has been proposed by O'Connor et al. involving cognitive-behavioral and psychophysiological elements [25]. This model describes an association between maladaptive beliefs about tics, premonitory urges, perfectionistic personality traits and negative psychophysiological consequences, such as elevated muscle tension in body areas where tics occur. The cognitive psychophysiological treatment developed by O'Connor et al. is a combination of sensorimotor activation and (meta-) cognitive interventions to target the proposed affected areas. So far, two open trials have been published in 36 adults and seven children with TS, indicating tic severity reduction after treatment [25, 26]. While being a possibly promising new treatment approach, RCT data are needed to determine the treatment effects.

Third-wave interventions

Third-wave interventions represent both an extension of and deviation from traditional cognitive-behavioral approaches, and include concepts such as metacognitive training, mindfulness and psychological flexibility, as part of behavioral treatments. The acceptance-based approach, which is shared by several third-wave interventions, prioritizes the promotion of health and well-being and suggests that rather than trying to control aversive psychological, emotional or physiological symptoms, accepting them might reduce their negative impact. [27]. So far, only a few studies have targeted the feasibility and efficacy of third-wave interventions for the treatment of patients with TS. A pilot study by Franklin et al. evaluated the feasibility of a combined treatment of HRT and acceptance and commitment therapy (ACT) in a small sample of adolescents with TS/CTD (N=13; 14–18 years), showing comparable results to traditional HRT [28]. Reese et al. tested the feasibility and efficacy of a modified form of mindfulness-based stress reduction (MBSR-tics) in a small open trial of adolescents and adults (16–67 years; N=18) with TS/CTD [29]. Fifty-nine percent of the participants were classified as treatment responders and results were maintained up to the 1-month follow-up. In a later study, Reese et al. modified the MBSR-tics intervention for online delivery [30]. In this open study (26–59 years; N=5), the intervention was judged feasible and acceptable. However, effects on tic severity and tic-related impairment from baseline to post-treatment were modest. The authors especially

point out that participant adherence to homework assignments, in this online format, was lower than anticipated.

The acceptance-based approach has also been tested with a focus on premonitory urge sensations. In an experimental study, 45 young people (8–17 years) participated in three different two-minute-conditions: free-to-tic (baseline), tic suppression and urge acceptance [31]. Results showed a significantly higher decrease in frequency and intensity of premonitory urges in the urge acceptance condition, compared to the other conditions. Additionally, the level of discomfort was found to be significantly lower during the urge acceptance condition compared to the tic suppression condition.

Another third wave intervention is *resource activation*, which has been evaluated in a within-subject pilot trial for young people (8–19 years; $N=24$) with TS/CTD [32]. The treatment focuses on the strengths and abilities of the patients and includes relaxation and mindfulness techniques. The trial showed significant reductions of tic severity and tic-related impairment, indicating that resource activation is a potentially effective treatment for patients with TS.

These pioneer studies indicate the potential feasibility of third-wave interventions for TS, however, RCTs are needed to determine efficacy and make recommendations for their use.

BT and PT

Only one RCT comparing the effects of BT to PT on tic severity has been published to date. Rizzo et al. randomized 110 young people (8–17 years) into three groups: BT (either HRT or ERP), PT (either risperidone, aripiprazole or pimozide), and psychoeducation [14]. Data were available for 102 participants (BT: n=25; PT: n=53; psychoeducation: n=24). At post-treatment, tic severity (as measured by the YGTSS-TTS) improved significantly in the BT and PT groups compared to the psychoeducation group (between-group effect sizes: 1.42 for BT and 0.84 for PT [calculated from data presented in the original article]). The larger effect size in the BT group compared to the PT group may partially be explained by differences in baseline tic severity. In the same vein, there were no significant differences between the BT and PT groups at the same measure, indicating that BT and PT potentially could be equally effective. While these results are important, replication studies are warranted given the limitations of this RCT. These include low statistical power to assess between-group differences in the three conditions and the lack of intention-to-treat data.

Originating from animal study findings, cognitive enhancers such as D-cycloserine (DCS) are hypothesized to strengthen newly learned associations, which in turn may augment the treatment effects of BT. In a preliminary RCT [33], McGuire et al. randomized 20 participants (8–17 years) to one session of HRT plus 50 mg of DCS or one session of HRT plus placebo. The study found a significant between-group effect (in favor of the HRT plus DCS-group) on the Hopkins Motor/Vocal Tic Scale, for the two bothersome tics targeted in the HRT treatment. Limitations include not providing a full dose of HRT treatment and not including the YGTSS as an outcome measure. Further studies are needed to establish the possibly augmenting effect of DCS on BT.

Meta-analyses of BT

In recent years, as more RCTs on the efficacy of BT have been published, a number of systematic reviews and meta-analyses have been undertaken [34–38]. The studies range from an early meta-analysis by Wile et al. [34] including 4 RCTs to the most recent meta-analysis by Yu et al. [38], which summarized 10 RCTs exclusively of HRT and CBIT. The latter meta-analysis included a total of 586 participants and found a medium effect size for HRT (SMD = 0.43). Additional subgroup analyses indicated no differences in the therapeutic effect comparing mode of delivery (face-to-face vs. online) or age group (children vs. adults). Notably, Yu et al. defined strict inclusion criteria, such as only including studies which employed the YGTSS, thus resulting in some earlier trials being excluded (e.g. [39]). A meta-analysis by McGuire et al. [35], which was published 6 years earlier, employed less strict criteria (summarizing 8 RCTs, with $N=438$), and reported a slightly larger medium effect size (SMD = 0.67) for BT.

Regarding other types of psychological interventions, a meta-analysis by Hollis et al. [36] found no evidence for tic-specific effectiveness of relaxation training, parent training, or anger control training.

Predictors and moderators of response to BT

A few studies have examined, primarily in a post-hoc fashion, predictors and moderators of response to BT for tic disorders. In a meta-analysis including pediatric and adult trials, McGuire et al. found that BT had larger treatment effects among trials with older average participant age, more therapy sessions, and with less co-occurring attention-deficit/hyperactivity disorder (ADHD), while concurrent PT for TS did not influence the treatment effects [35]. However, findings regarding the impact of ADHD on therapy are equivocal. Conelea et al. [40], using data from experimental settings, showed that young people (5–17 years) with ADHD can suppress tics just as effectively as those without ADHD.

Sukhodolsky et al. examined predictors and moderators of treatment in BT and PST [41]. The study showed that positive participant expectancy and greater tic severity predicted greater tic improvement in both groups, while comorbid anxiety disorders and greater premonitory urge severity predicted a lower tic improvement [41]. The

presence of PT for TS predicted tic reduction in the PST group, but not in the BT group. Taken together, the available studies suggest that PT for TS does not influence the treatment effects of BT. In another study, based on data from the same original RCTs as used in the Sukhodolsky et al. study, Essoe et al. concluded that adherence to homework assignments predicted tic reductions and treatment response [42].

Using data from a randomized trial evaluating a combination of HRT and ERP (described in more detail in a later section) [43], Nissen et al. investigated possible predictors and moderators of treatment response [44]. Their data suggest that internalizing symptoms (anxiety) predicted a lesser reduction in functional impairment and that participants' (negative) beliefs about their tics were shown to have a negative effect on treatment outcome.

More studies are needed to replicate and further deepen the understanding of potential predictors and moderators of response to BT for patients with TS.

Neurobiology of BT

So far, only one study has investigated neurobiological changes following the use of BT in TS. Deckersbach et al. [45] used functional magnetic resonance imaging (fMRI) to investigate 8 subjects who participated in a large CBIT trial [15] matched with 8 healthy controls. fMRI was conducted pre- and post-treatment in conjunction with a visuospatial priming task to measure response inhibition. The authors found a decrease of striatal activation in the putamen at the post-treatment assessment, which formed a hypothesis that BT leads to a normalization of activation in the putamen. A further finding was a negative correlation between change in tic severity (as measured by the YGTSS-TTS) and a region in the inferior frontal gyrus. A similar more recent study by Petruo et al. [46] used an inhibitory control task to investigate the hypothesis that patients with TS ($n=21$) exhibit an increased perception–action binding [47] as compared to healthy controls ($n=21$). Indeed, patients exhibited an impaired performance on the task at baseline, which was normalized after the CBIT intervention.

Novel modalities of established behavioral treatments

Given the limited availability of therapists trained in delivering BT for patients with tic disorders [48], focus on dissemination and adaptation of treatment delivery has increased in recent years. New modalities have been proposed to make BT more accessible, primarily by reducing the number of therapists needed and/or reducing the need for travel. The modalities fall into three main areas: group delivery; videoconference delivery; and internet delivery. Additionally, there are case series using intensive treatment delivery schedules to reduce travel time.

Group delivery of BT

Group delivered BT for patients with TS has emerging evidence to date. Yates et al. compared two 8-session group interventions (CBIT [$n=17$] vs psychoeducation [$n=16$]) among children (9–13 years) with TS [49]. The results showed a reduction in motor tic severity at post-treatment (effect size: 0.55, in favor of the CBIT group). None of the groups showed a significant reduction in vocal tic severity. The observed treatment effects on tic severity and quality of life were maintained at a 12-month follow-up [50]. Interestingly, both groups reported a higher rate of school attendance in the year following treatment as compared with the year before the intervention. In this study, meeting other young people with tics did not increase tic expression, which is a common fear expressed by parents and patients.

Zimmerman-Brenner et al. [51] compared group-delivered CBIT to group-delivered psychoeducation in a RCT (8–15 years; $N=61$). Participants received 8 weekly sessions during the acute treatment phase and 3 additional monthly sessions during a 3 months follow-up phase. Results showed no significant between-group effect on the YGTSS-TTS at post-treatment, but significant within-group improvements on the YGTSS Motor Tic Severity Score and the YGTSS Impairment Score for both groups. Interestingly, tic severity as measured by the YGTSS-TTS increased in both groups at post-treatment. This effect was seemingly driven by a significant increase in vocal tic severity, which could have been a side effect of the group format. At the 3-month follow-up, however, both groups showed improved YGTSS-TTS scores compared to baseline, indicating that the worsened vocal tic severity was temporary. Further, only the CBIT group showed a maintained improvement on the YGTSS Motor Tic Severity Score at the 3-month follow-up, indicating a possible benefit for this active treatment.

Nissen et al. conducted a randomized trial comparing a combination of HRT and ERP in young people (9–17 years; $N=59$) in either an individual setting or a group setting [43]. Both settings involved nine sessions, where HRT was introduced before ERP, and the final sessions were devoted to the type of BT that seemed most effective for that specific participant. The study showed significant tic severity reductions in both settings (within-group effect sizes: 1.21 for the individual setting and 1.38 for the group setting). A total of 66.7% of the participants were considered treatment responders (defined as a 25% reduction on the YGTSS-TTS). There was no statistically significant difference between the groups, apart from the YGTSS Impairment Score (in favor of

the individual setting). The within-group treatment effects were maintained for both groups at a 12-month follow-up [52].

Lastly, in an open pilot study by Heijerman-Holtgrefe et al. [53] (9–14 years; $N=14$), ERP was evaluated in an intensive group format (12 sessions fitted into 3 + 1 days). This so-called *"Tackle your tics"*-programme further included coping strategy workshops led by young adult patients, relaxation training, and separate parent meetings. The results showed a significantly decreased tic severity (YGTSS-TTS) between baseline and a 2-month follow-up ($\eta_p^2=0.41$), increased quality of life and high treatment satisfaction.

To summarize, studies of group delivery of BT have shown mixed results. More studies are needed to make firm recommendations for clinical practice.

Videoconference delivery of BT

Videoconference BT is identical to regular face-to-face BT, except for that the (real time) communication between the patient and therapist is made via videoconference software. Two pilot RCTs have evaluated CBIT via videoconference delivery [54, 55]. Himle et al. compared videoconferencing (received at a clinic) to face-to-face delivery (8–17 years; $N=20$) and found that tic severity was reduced regardless of the CBIT modality, with similar within-group effects at a 4-month follow-up [54]. Ricketts et al. compared videoconferencing (received at home via the software Skype) to a waiting-list control condition (8–16 years; $N=20$), and found a greater tic severity reduction in the videoconferencing group, compared to the waiting list condition [55]. Although some challenges (like video/audio problems and difficulties viewing homework) were described [55], both studies reported strong therapeutic alliance ratings, treatment satisfaction, and videoconferencing satisfaction in the videoconferencing groups [54, 55]. These findings suggest that videoconferencing is a feasible and acceptable format for the delivery of BT for young people with TS. Larger controlled studies are, however, needed to determine the clinical efficacy of this format.

A perhaps related treatment delivery format, where a DVD is provided to the patient with instructions on how to perform HRT (with support of a parent), has been tested in a pilot randomized controlled trial (7–13 years; $N=44$) [56]. Both the DVD-HRT group and the comparison face-to-face-HRT group showed improvements on the YGTSS-TTS in a within-group analysis. Results are, however, difficult to interpret due to large dropout rates and the lack of an intention-to-treat analysis.

Internet delivery of BT

In internet-delivered BT, patients work through a self-help programme briefly supported by a therapist (via text messages or telephone). A Swedish internet platform called BIP (Barninternetprojektet [The Child Internet Project]) has successfully been used to deliver such internet-delivered treatment for several pediatric mental health conditions [57, 58]. Andrén et al. used the BIP-platform to evaluate two therapist-guided internet-delivered interventions based on HRT and ERP principles (called BIP TIC HRT and BIP TIC ERP) in a pilot trial (8–16 years; $N=23$) [59]. Both interventions showed a significant reduction in tic-related impairment and parent-rated tic severity, but only BIP TIC ERP showed a significant improvement in clinician-rated tic severity as assessed by the YGTSS-TTS (within-group effect sizes at the 3-month follow-up: BIP TIC ERP: 1.12; BIP TIC HRT: 0.50). Therapeutic gains were maintained at the 12-month follow-up. An additional advantage of the treatment format was that it demanded less therapist time (approximately an average of 25 min per participant per week, mainly via text messages) than traditional face-to-face BT.

In an Israeli RCT (7–18 years; $N=45$) [60], Rachamim et al. compared internet-delivered CBIT to a waitlist condition. The results showed a large, significant between-group effect on the YGTSS-TTS ($\eta_p^2=0.20$; in favor of internet-delivered CBIT). The active group was followed until 6 months post-treatment, where it showed a large within-group effect on the YGTSS-TTS ($d=2.25$). Also in this study, therapists spent considerably less time with patients (ca. 7 min per participant per week, via telephone) than in traditional face-to-face BT.

Treatment intensity

Studies have explored the benefits of delivering treatment in an intensive and brief manner, potentially making treatment more efficient and convenient for patients who travel long distances to receive care. Blount et al. piloted an intensified version of the CBIT-protocol (several hours of daily treatment over a 4 day period, called IOP CBIT) in two boys (ages 10 and 14 years) with TS, showing a tic reduction which was maintained up to 6 and 7 months later [61]. Along the same line, van de Griendt et al. addressed the question of whether shorter sessions of ERP (1 h compared to the 2 h used in the Verdellen et al. RCT [9]) would yield a different treatment outcome [62]. Results suggest that shorter sessions were not inferior to longer sessions regarding tic severity outcomes, implicating the clinical use of shorter sessions to accommodate more treatment delivery within the same time frame [62]. Chen et al. evaluated the effects of a shortened CBIT-protocol (four instead of eight sessions). In a RCT [63], 46 participants (6–18 years) were randomized to shortened CBIT plus usual care (psychoeducation and 50 mg of pyridoxine) or usual care only. Results showed a medium-sized, significant between-group effect on the YGTSS-TTS (in favor of CBIT plus usual care; d=0.56). The CBIT plus

usual care-group further improved in a within-group analysis at a 3-month follow-up. This study provides preliminary evidence for CBIT being efficacious also in half of the previously evaluated dose. A final example of a shortened CBIT-protocol is the previously reported study by Bennett et al [21], where the treatment was shortened from 8 to 6 sessions for their very young sample (5–8 years), and still was shown to be efficacious. Another example of a more intensive treatment approach is the previously mentioned *"Tackle your tics"*-programme [53]. Further studies are needed to evaluate the intensity, spacing and duration of treatment sessions on the efficiency and effectiveness of BT.

Survey on the use of psychological interventions among TS health care providers

As part of these European clinical guidelines, between October and November 2019, the ESSTS working group conducted a survey among 59 ESSTS members and TS experts. Compared to a previous similar survey conducted in 2011, the current survey showed that the popularity of psychological interventions increased over the course of eight years. In 2011, 47% of experts considered BT as a first-line intervention. In the current survey, the experts' preference for BT as a first-line intervention increased to 63% (in the case of adults) and 79% (in the case of children). In 2011, no difference was made between children and adults. For medication, the opposite trend was observed. In 2011, 35% of the experts considered medication a first-line intervention, which dropped to 12% in adults and 5% in children in the 2019 survey. In the current survey, 80% of the experts stated that BT was available in their region for children, 59% stated that it was available for adults, while 15% stated it was unavailable. While that number seems relatively high, it would be wrong to imply that the supply met the demand in those regions. According to the experts' estimations, only about 52% of the patients who were recommended BT actually had access to it. This resembles the findings of the 2011 survey, where 20 out of 40 respondents (50%) reported having difficulties in finding a knowledgeable provider for BT. Various modalities of treatment delivery were available in routine clinical care in the respondents' regions, primarily individual face-to-face treatment (80%), and to a lesser extent internet-delivered treatment (22%), and group-delivered treatment (19%). Equivalent data were not available in the 2011 survey.

Recommendations

Clinical consensus follows that psychoeducation is essential to help the patient and his/her environment to understand the condition and make well-informed treatment decisions. Psychoeducation is therefore recommended as the initial intervention for all individuals who are diagnosed with TS. Psychoeducation can be delivered without specialist training in psychotherapy. It should be individualized and meet the needs of the individual patient and his/her family. In cases where psychoeducation is judged to be a sufficient intervention for the patient, it is appropriate to adopt a *watch and wait* approach.

When psychoeducation alone is insufficient, BT (more specifically HRT/CBIT and ERP) is recommended as a first-line intervention for children and adults with tic disorders. Of the two BT interventions, HRT/CBIT has the strongest evidence-base. In the 2011 European clinical guidelines, several RCTs were reported which showed HRT/CBIT to be superior to various control conditions, of which the Piacentini et al. [8] pediatric trial currently is the largest study ($N = 126$). Since then, one major RCT ($N = 122$) has been published, showing that HRT/CBIT also is an effective treatment for adults [15]. Since 2011, no new RCTs have evaluated the use of ERP as a treatment for patients with TS. Based on one RCT [9], ERP is recommended as a treatment for patients with tic disorders, but at a lower certainty than HRT/CBIT due to considerably fewer published studies. To date, there is no appropriate evidence-base to make a differential indication as to when to apply HRT or ERP in particular. Verdellen et al. [9] report that "at face value" patients with a higher number of tics as assessed via the YGTSS dimension "Number of tics" could benefit more from ERP, since this method allows for a simultaneous treatment of multiple tics. Van de Griendt et al. [64] discussed from a theoretical point of view, that in the case of no tics and urges being present nor evocable during a therapy session, HRT could still be practiced and explained to the patient, while ERP could not properly be conveyed. Another theoretical point is that ERP could be given a preference in patients with comorbid obsessive–compulsive disorder (OCD) since ERP is the primary treatment for OCD [65]. In summary, there are no evidence-based indications as to when HRT or ERP is indicated. Clearly, future studies are necessary to provide an indication of what intervention works best for whom. For detailed information on how to deliver HRT/CBIT or ERP, including information on session amount and duration, see the published treatment manuals (e.g. [12, 13]).

Due to a current lack of controlled studies, cognitive interventions and third-wave interventions are not recommended as stand-alone treatments for patients with TS. However, it could be reasonable to offer such treatments as second-line interventions (or augmentations), if HRT/ERP has shown insufficient results and other evidence-based treatments (such as PT) are not available/possible or preferred by the patient. Notably, third-wave interventions have been shown to be effective treatments for other conditions, which are often co-occuring with tic disorders [66]. ACT has

been shown to be effective for depression, anxiety, addiction and psychosomatic problems [67]. An improvement in any of these comorbid conditions could potentially, indirectly, contribute to an improvement of tic severity.

No new studies have been published on the efficacy of relaxation techniques (RT) since 2011. Because of a lack of sufficiently powered controlled studies the recommendation of RT is limited to a second-line intervention. An overview of the evidence on the efficacy of RT can be found here [68].

Since the 2011 European clinical guidelines were published, new treatment formats have been evaluated for the delivery of BT. At the moment, most evidence is found for videoconference delivery, which has been evaluated in two small RCTs [54, 55]. Additionally, there are some pilot data supporting the formats of group delivery and internet delivery, but more studies are warranted to enable firm recommendations.

Current knowledge gaps and future directions

HRT/CBIT s is the psychological intervention for patients with TS that has the broadest evidence-base. A limitation of previously published trials of HRT/CBIT is that analyses on long-term durability have been limited to treatment responders and completer data [8, 15]. Due to tic disorders' natural waxing and waning course, it is especially important to conduct well-controlled studies with long-term follow-up, using an intention-to-treat approach. For ERP to be recommended with the same certainty as HRT/CBIT, large RCTs in which ERP is compared to appropriate control conditions are warranted.

Regardless of the documented positive effects of BT, there is still room for improvement in the efficacy and efficiency of treatment delivery. In the two largest trials of BT (HRT/CBIT), reported between-group effect sizes were within the medium range (0.57 and 0.68) [8, 15]. Tic severity was reduced by 26–31% (as measured by the YGTSS-TTS), implicating that patients may still experience severe tics after being treated with BT. One way to make treatments more effective and efficient is to gain a better understanding of the underlying working mechanisms of BT. While studies of habituation as a working mechanism of BT for tics are equivocal [69, 70], other potential mechanisms should be empirically examined, e.g. urge tolerance, disconfirmation of beliefs that unpleasant urges cannot be tolerated, and increased inhibitory control [71, 72]. Enhancing the efficacy and efficiency of BT could also be done by studying predictors and moderators of treatment response, ways to increase treatment adherence, or the effects of booster sessions. Furthermore, it is unclear if and how the working mechanisms of HRT and ERP differ from each other, and whether combined approaches (such as studied by Nissen et al. [43]) or sequential/add-on approaches (such as studied by Verdellen et al. using a cross-over design [9]) offer additional benefits. Further, the added value of the generic interventions originating from functional analysis and/or relaxation as used in CBIT, needs to be addressed. Related to this, psychoeducation is also included in BT protocols, as well as being recommended as an initial intervention (prior to BT), but has not yet been evaluated in its own right, for example against a waitlist. From a theoretical perspective, a further understanding of the underlying learning processes and neurobiological correlates in TS treatment might be beneficial for improving BT for patients with TS.

The limited availability of BT for TS has led to an increased focus on dissemination and adaptation of treatment delivery in recent years. The ESSTS survey indicated that BT is fairly widely available now in the regions of ESSTS members (although more available for children than adults), but caution is warranted when interpreting these results since data primarily originated from specialist clinics. To further overcome geographical barriers and the lack of trained therapists, remote delivery of BT might be a solution. Especially, in the light of the currently ongoing COVID-19 pandemic, all forms of videoconferencing and internet-delivered interventions are becoming more vital. To our knowledge, three ongoing RCTs are currently evaluating two different internet-delivered BT interventions: internet-delivered CBIT without therapist support (called ONLINE-TICS, which is being evaluated in Germany [73]), and therapist-supported internet-delivered ERP (called BIP TIC ERP, which is being evaluated in both the UK [74] and Sweden [75]. Another ongoing RCT is evaluating group delivery of BT and modifications of treatment intensity [76]. Time will tell, if any of these modalities will become evidence-based interventions for patients with tic disorders.

RCTs of BT and RCTs of PT show roughly comparable effect sizes for both treatments (e.g. 0.57–0.68 for CBIT/HRT compared to PST, and 0.45–0.79 for various compounds of PT compared to placebo) [11, 77]. The recommendation of BT as a first-line treatment is based on the fact that BT has shown fewer (and less severe) side effects and longer-lasting treatment effects than PT (which are expected to dissipate with drug discontinuation). However, to be more precise about the differences in effects, side effects and sustainability of effects, RCTs comparing BT to PT head-to-head are needed. Furthermore, studies are needed to determine which TS patient will most likely benefit from either treatment. A small-scale RCT comparing ERP with risperidone is currently being conducted in terms of short- and long-term efficacy, cost-effectiveness, side effects and dropout rates [78]. In addition, the (potentially additional) effect of combining BT and PT needs to be studied further.

Comorbidities are common among individuals with TS, which implies a strong likelihood that clinicians delivering treatment for TS will need to consider making treatment adaptations to accommodate for one or several comorbid psychiatric disorders. Currently, data is lacking on how psychological treatments for TS should be adapted. This area needs to be studied to generate recommendations regarding the treatment of TS when comorbid conditions are present.

Conclusions

Based on clinical consensus, psychoeducation is recommended as an initial intervention for all individuals who are diagnosed with TS. A *watch and wait* approach could be reasonable for patients without functional impairment from their tics, also considering that many young people likely experience a natural decrease in tics over time. When psychoeducation is insufficient, BT (HRT/CBIT and ERP) is recommended as a first-line intervention for children and adults with TS, if available. When comorbid psychiatric conditions are present, clinicians must adopt a pragmatic approach to guide decision-making on treatment adaptation and prioritization of what symptoms should be treated first. If there are unsatisfactory effects from BT, switching from one behavioral intervention (HRT/CBIT or ERP) to another or switching to PT can be considered. Alternatively, BT could be augmented with PT. Clinicians should also be aware that not all patients are motivated to undergo BT, hence it is important to always take each patient's preferences into consideration. A decision tree summarizing all treatments recommended by the European clinical guidelines for patients with TS is presented in an editorial in the current issue of this journal.

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REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

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Abstract
In 2011, the European Society for the Study of Tourette Syndrome (ESSTS) published the first European guidelines for Tourette Syndrome (TS). We now present an update of the part on pharmacological treatment, based on a review of new literature with special attention to other evidence-based guidelines, meta-analyses, and randomized double-blinded studies. Moreover, our revision took into consideration results of a recent survey on treatment preferences conducted among ESSTS experts. The first preference should be given to psychoeducation and to behavioral approaches, as it strengthens the patients' self-regulatory control and thus his/her autonomy. Because behavioral approaches are not effective, available, or feasible in all patients, in a substantial number of patients pharmacological treatment is indicated, alone or in combination with behavioral therapy. The largest amount of evidence supports the use of dopamine blocking agents, preferably aripiprazole because of a more favorable profile of adverse events than first- and second-generation antipsychotics. Other agents that can be considered include tiapride, risperidone, and especially in case of co-existing attention deficit hyperactivity disorder (ADHD), clonidine and guanfacine. This view is supported by the results of our survey on medication preference among members of ESSTS, in which aripiprazole was indicated as the drug of first choice both in children and adults. In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse effects might be considered, including pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections. Overall, treatment of TS should be individualized, and decisions based on the patient's needs and preferences, presence of co-existing conditions, latest scientific findings as well as on the physician's preferences, experience, and local regulatory requirements.

Keywords Tics · Tourette syndrome · Pharmacotherapy · Medication · Treatment

Introduction

The first European clinical guidelines for Tourette Syndrome (TS[1]) were published in 2011 [1] by working groups of the European Society for the Study of Tourette Syndrome (ESSTS) and provided recommendations for the assessment and treatment of TS based on existing guidelines, meta-analyses, reviews, clinical trials, and case studies up to that point. The present guideline provides clinicians an update of recommendations for the pharmacological treatment of TS in Europe using evidence from clinical trials and clinical expertise.

In general, clinical guidelines rely on the combination of information from controlled clinical trials (including their shortcomings) and clinical (consensus-based) knowledge, given the lack of sufficiently comprehensive and detailed evidence. Regarding TS, the situation mentioned in our 2011 article with "…only a limited number of studies on pharmacological treatment options for TS met rigorous quality criteria…" still holds true. Especially head-to-head comparisons of different agents or their combination as well as optimal treatment duration and dosage have not been systematically

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[1] We use the term TS in these guidelines, wherever information also applies to other forms of tic disorders. Only if there are substantial, well-known differences between TS and other forms of tic disorders we use TS or other terms, e.g. transient or chronic motor tic disorder.

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investigated, hence calling for an approach supplemented by knowledge from clinical practice. Moreover, the effectiveness of pharmacological treatments in reducing tics varies between trials as a result of differences in methodology and patient characteristics. Furthermore, controlled studies in treatment resistant cases are lacking. It remains common practice to have to try various options until an effective reduction of tics is achieved [2].

Recently, a systematic review and guidelines of the American Academy of Neurology (AAN) for the treatment of TS have been published [3, 4]. The authors of the AAN guidelines used structured, evidence-based methodology as outlined in the 2011 edition of AAN's guideline development process manual. To formulate new European recommendations for the pharmacological treatment of TS, we complemented the English-language literature since 2011 and combined it with the results of a survey among ESSTS experts, who were asked about their pharmacological daily practice in children and adults with TS.

Methodology of selection of agents and literature search strategy

To select relevant agents, we combined agents with at least moderate or low evidence according to the guidelines of the AAN [3, 4] with those mentioned in our European survey. For these agents, we reviewed the English-language literature since 2011 in PubMed using the agent's name in combination with "tics", "tic disorder", or "Tourette Syndrome", including children, adolescents, and adults as search string. In addition, we checked the references since 2011 of other systematic reviews/meta-analyses [5–9], existing guidelines [3, 4, 10–12], non-systematic reviews on TS with statements about pharmacological treatment, i.e., dealing with various agents [13–38] or mentioning treatment in their title [39–64]. In addition, we had a look into the references of agent-specific reviews and meta-analyses of (in alphabetical order) aripiprazole [65–72], atypical antipsychotics [73], botulinum toxin [74–85], cannabis [86–88], clonidine [89, 90], complementary alternative medicine [91], deutetrabenazine [92], non-dopaminergic agents [93], traditional Chinese medicine [94], and topiramate [95, 96]. Moreover, we screened references of reviews on specific aspects of TS if they describe treatment options for co-existing attention deficit hyperactivity disorder (ADHD) [97–103], obsessive–compulsive disorder (OCD; [104, 105], autism and stereotypies [106, 107], adverse events of pharmacological treatment in TS [108, 109], and treatment resistant TS [110].

Agents from recently published AAN guidelines

The authors of the AAN guidelines included only systematic reviews and randomized controlled trials (RCTs) on the treatment of tics that included at least 20 participants. They concluded that there is "….moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, botulinum toxin injections, 5-ling granule, and Ningdong granule were probably more likely than placebo to reduce tics….". Lower confidence was reported for pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol (THC). Strong confidence was demonstrated only for behavioral approaches for tics (for detailed description of the behavioral approaches consult Part II of our guidelines).

Agents mentioned in the ESSTS survey

In the survey of the ESSTS Guidelines Group conducted in 2019, ESSTS experts' prescription practices for the treatment of TS were gathered. They were asked which medication they would consider as first, second, third, and subsequent choices, provided absence of contra-indications for the available agents and absence of co-existing conditions. Contrary to our prior survey from 2011 [111], we also asked the experts to give their recommendations separately for children/adolescents and adults.

In general within the answers of 59 clinicians, choices in children/adolescents did not differ from those in adults and pointed to a high preference for aripiprazole in both age groups. The main difference between the age groups was that haloperidol was much more commonly considered in adults, while in children/adolescents tiapride was more often mentioned (for details consult, Table 1). When comparing the results of our ESSTS surveys performed in 2011 and in 2019, a clear shift over the last decade can be seen from risperidone, pimozide, and (ami)sulpiride in favor of aripiprazole (Fig. 1).

We also collected experts' opinion on the reason for starting pharmacological treatment of TS. Fifty-nine clinicians treating patients with TS who were members of ESSTS (95% from Europe) regarded as most important reason that the "patient/parents requested medication", followed by "behavior therapy had not been successful", and finally "high severity of tics". While 81% of clinicians would use pharmacotherapy as first-line to treat severe tics, in the case of moderate tics this was done only by 34%, and in the case of mild tics by 3% of clinicians (for detailed description of the survey's results consult Part V of this issue).

Selection of agents to be discussed in detail

From the moderate confidence group in the AAN guidelines [3] all agents except 5-ling granule and Ningdong

Table 1 Preferences of agents for treatment of TS

Children and adolescents ($n = 15$ different agents were given)			Adults ($n = 14$ different agents were given)		
Points	Percentage		Points	Percentage	
141	29.2	Aripiprazole	127	31.0	Aripiprazole
82	17.0	Clonidine	70	17.1	Haloperidol
81	16.8	Tiapride	37	9.0	Clonidine
49	10.1	Guanfacine	32	7.8	Risperidone
25	5.2	Atomoxetine	26	6.3	Quetiapine
20	4.1	Risperidone	20	4.9	Botulinum toxin
18	3.7	Topiramate	17	4.1	Cannabinoids
18	3.7	Cannabinoids	14	3.4	Pimozide
15	3.1	Pimozide	11	2.7	Guanfacine
11	2.3	Amisulpiride	11	2.7	Amisulpiride
8	1.7	Tetrabenazine	10	2.4	Topiramate
5	1.0	Quetiapine	10	2.4	Atomoxetine
4	0.8	Haloperidol	9	2.2	Tetrabenazine
3	0.6	Botulinum toxin	8	2.0	Tiapride
2	0.4	Sertraline	8	2.0	Sertraline
1	0.2	Sulpiride			
483	100		410	100	

Choices are given separately for children/adolescents and adults. We received 50 responses for children/adolescents and 45 responses for adults (from 50 ESSTS experts; overlap in many cases). 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. To enable a comparison of the preferences between both age groups we calculated percentages

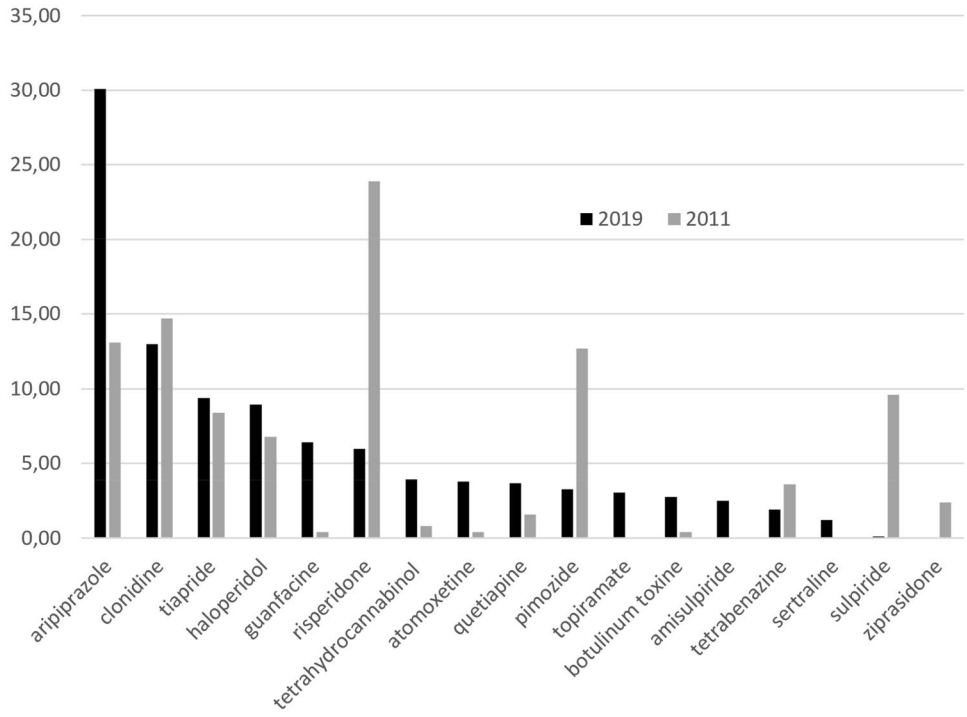

Fig. 1 Results from ESSTS surveys on preferences of agents for the treatment of tics in 2011 compared to 2019. In 2011, responses from 22 TS experts were received, while in 2019 50 ESSTS experts (45 responses for treatment in adults and 50 in children/adolescents, findings shown together). Each first choice agent was rated with 4 points, a second-choice agent with 3 points, a third-choice agent with 2 points, and additional agents with 1 point. In 2011, 1 point was given for desipramine, thioridazine, oxcarbazepine (not shown in the figure)

granule were commonly prescribed by ESSTS experts (see Table 1). From the lower confidence group only ziprasidone and metoclopramide were not prescribed by ESSTS experts. Vice versa, amisulpiride, tetrabenazine, quetiapine, sertraline, atomoxetine, and sulpiride were mentioned by ESSTS experts as prescribed agents but not in the list of agents with

at least moderate or low evidence according to the AAN guidelines.

Dysfunction of transmitter systems as basis for psychopharmacological treatment

TS has been associated with a dysfunction of many neurotransmitter systems, especially the dopaminergic system [39, 112]. Based on findings from nuclear imaging studies, four hypotheses on dopamine dysfunction in TS have been postulated: (1) dopamine hyper-innervation within the striatum; (2) supersensitive postsynaptic striatal dopamine receptors; (3) presynaptic dopamine abnormality in dopa carboxylase; and (4) elevated intrasynaptic dopamine release as a result of an imbalance between tonic and phasic dopamine levels [112]. Besides a dysfunction in the dopaminergic system, imbalances in other neurotransmitter systems have been suggested including serotonergic, noradrenergic, glutamatergic, GABAergic, cholinergic, histaminergic, endocannabinoid, and opioid systems [34, 39]. These findings give some rationale to use substances other than dopamine blocking drugs particularly for the treatment of tics resistant to dopamine-modulating agents.

Dopamine-modulating agents

The first agents used in treating tics were first-generation antipsychotics approved by the Food and Drug Administration (FDA), e.g. haloperidol (in 1969) and pimozide (in 1984), whereas aripiprazole was approved in 2014. In European countries, only haloperidol has been licensed for TS [113]. Discrepancies concerning the licensing of the same agents in Europe and the US largely stem from differences in interests of pharmaceutical companies between the US and Europe. In general, adverse effects of dopamine receptor antagonists are broad, ranging from extrapyramidal adverse effects including acute dystonia, parkinsonism, and akathisia to metabolic adverse effects including weight gain, type 2 diabetes mellitus, lipid spectra abnormalities, blood pressure changes, fatigue, headache, body temperature dysregulation, hyperprolactinemia, and sexual dysfunction, increase of prolactin levels, and QTc-prolongation as well as 'behavioral' changes, such as concentration problems, apathy, anhedonia and sedation, aggression, anxiety, and agitation [114, 115]. The limited existing evidence does not allow to predict individual potential adverse effects preceding the start of treatment [116]. Regarding hyperprolactinemia, antipsychotics with tight D2-binding predictably lead to hyperprolactinemia ("prolactin-raising"), whereas antipsychotics with loose D2-binding and partial agonistic action (e.g., aripiprazole) are considered as "prolactin-sparing" [117]. While most experts recommend measurement of prolactin levels before and during treatment with antipsychotics, long-term effects of hyperprolactinemia on sexual, bone, and breast development without accompanying acute clinical symptoms are unknown. Accordingly, the question of whether switching to another antipsychotic only because of hyperprolactinemia (without any clinical symptoms) is still a matter of debate [109, 118].

First-, second-, and third-generation antipsychotic agents are all being used in TS. First generation antipsychotics show predominantly extrapyramidal adverse effects and sedation, while second-generation drugs have more metabolic adverse effects (i.e., weight gain, disturbed blood lipid spectra, a higher risk of diabetes, and other metabolic adverse effects [108, 119, 120]). Second- and third-generation antipsychotics are more widely used and have a mode of action that is distinct from first generation antipsychotics' mode of action, by their binding to both dopamine and 5-HT2 receptors, i.e., their 5-HT2A receptor antagonism [51]. In line with this observation and despite the absence of regulatory approval for their use in TS for the majority of agents (with the exception of aripiprazole in the US), treatment recommendations favor the use of newer generation antipsychotics rather than first generation antipsychotics as first line treatment for tics, predominantly because of a more favorable tolerability with respect to extrapyramidal adverse effects [111, 115, 121]. In the following paragraphs we review the various antipsychotics that may be used as treatment of TS.

First-generation antipsychotics

Haloperidol

Haloperidol was the first antipsychotic medication proven to be effective in the treatment of TS and is in the EU still the only agent with approval for TS. It is a potent dopamine antagonist, specifically against dopamine D2 receptors. It also blocks muscarinic acetylcholine receptors as well as adrenergic receptors and has a well-documented effectiveness in tic reduction [6, 111]. Since 2011, no new English-language RCTs have been published in TS. The most recent meta-analysis (including also Chinese-language RCTs) of haloperidol as treatment for TS pointed to a standardized mean difference compared with placebo of 3.20 (95% CI [0.14–6.52]) [6].

However, due to considerable adverse effects (particularly parkinsonism, apathy, anhedonia, and QTc-prolongation), the use of haloperidol as treatment of TS has decreased within the last three decades from being a first-line agent to being used only in carefully selected, severely affected, and otherwise treatment resistant patients [3, 4, 10].

Pimozide

Pimozide is a dopamine D2 receptor antagonist which also blocks calcium channels. In the past, it has been one of the most frequently used medications in the treatment of tics [115] despite only a limited number of trials comparing its effectiveness to placebo or other agents [122]. Since 2011, no new English-language RCTs have been published in TS. Although several reviews give some support that pimozide is effective as treatment of tics, a recent meta-analysis (including also Chinese-language RCTs) did not find that pimozide is significantly better than placebo [6]. Moreover, due to its prominent adverse effects including drowsiness and risk of extrapyramidal symptoms (EPS), although to a lesser extent as compared to haloperidol [9, 122], weight gain (less than risperidone, but more than aripiprazole), sedation [9, 122–124], and the risk of QTc prolongation [9, 122], its application has declined noticeably [125]. Similar to haloperidol, in current guidelines it is recommended only in severely affected and otherwise treatment resistant patients [10, 12].

Second- and third-generation antipsychotics

Risperidone

Risperidone acts through a dopamine D2 receptor and 5-HT2 receptor antagonism [126]. It is one of the best studied antipsychotics for the treatment of tics [16].

Three systematic reviews [8, 9, 90] describing the effect of risperidone on tics have been published since 2011, indicating that risperidone is effective in reducing tics. The most recent meta-analysis (including also Chinese-language RCTs) of risperidone as treatment for TS pointed to a standardized mean difference compared with placebo of 3.47 (95% CI [0.37–6.87]) [6]. One RCT [127] in 60 subjects compared the effects of aripiprazole and risperidone in children and adolescents over a 2-month period, with the conclusion that both medications were tolerated well, with equal effectiveness and similar adverse effects, including increased appetite in over 25% of the participants for either agent. Risperidone, in contrast, was superior in improving the patients' social functioning in the short term.

In terms of adverse effects, 35% of children with tics using risperidone developed EPS in a prospective longitudinal study on antipsychotic safety monitoring [128]. Risperidone-related weight gain seems to follow a pattern with a significant increase of body mass index (BMI) in the first month, followed by only a slow increase thereafter [129, 130]. Increase of prolactin levels was present in 41% of the children treated for tics [128].

Aripiprazole

Aripiprazole reduces dopaminergic neurotransmission through D2 partial agonism [131–133]. Thus, it modulates neurotransmission in dopaminergic (mainly mesolimbic and mesocortical) pathways. In addition, it is a partial 5-HT1A agonist and a 5-HT2A antagonist [131–134]. Aripiprazole has become a frequently used agent for the treatment of tics due to its good effectiveness on tics and less prominent adverse effects [50, 69, 72, 73, 111, 135].

Until 2011, the use of aripiprazole was only reported in case studies, retrospective observational studies, and open-label trials [51]. Thereafter, aripiprazole has become the main focus in research on the pharmacological treatment of tics: seven systematic reviews including five meta-analyses or combinations of the two [6, 8, 66, 68, 69, 71, 72] and two placebo controlled RCTs [136, 137] have been published since 2011. All publications consistently documented the effectiveness of aripiprazole in reducing tics, with similar effect sizes as compared to other dopamine-modulating agents, such as haloperidol and risperidone [6, 127, 138]. The most recent meta-analysis (including also Chinese-language RCTs) pointed to a standardized mean difference of aripiprazole compared with placebo of 4.74 (95% CI [1.06–8.67]) [6]. Moreover, there is some evidence from an open-label study that aripiprazole may also have a positive effect on co-existing conditions, such as depression, anxiety, and auto-aggression in adults with TS [135], as well as on social adjustment and parental stress [139]. However, it may have an unfavorable effect on complex learning tasks [140].

Aripiprazole has a more favorable profile of adverse effects compared to other antipsychotics with lower risk of akathisia and other EPS, anxiety, constipation, dizziness, headache, insomnia, nausea, and vomiting in patients with TS [6, 8, 111, 137]. Based on a study in children and adolescents with TS, aripiprazole has a safer cardiovascular profile than pimozide, with a lower frequency of QTc prolongation [125]. Importantly, aripiprazole is less sedating than most other antipsychotics in patients with psychosis [141]. However, more recent literature showed a mean EPS incidence of 17.1% (95% CI 12.8–22.3%) in children and adolescents with a variety of psychiatric disorders treated with aripiprazole [142]. As described in other antipsychotic agents, children gain more weight due to aripiprazole than adolescents and adults [120, 137], but among all antipsychotics aripiprazole has a relatively favorable metabolic profile [143].

Benzamides

Tiapride

Tiapride, a benzamide with low antipsychotic action, acts as a selective dopamine antagonist at dopamine D2 and D3

receptors. Despite its frequent use, particularly in German speaking Europe, the evidence on its effectiveness in the treatment of tics in controlled trials is still sparse [52, 144]. While tiapride is not available in the US [145], in recent years, there was a growing interest in this agent in other countries, such as China [6, 138] and two Chinese guidelines recommended tiapride as first-line medication (Chinese medical association [11]; Chinese Child Neurology Society [12]).

Since 2011, there has been one new English-language RCT [138] and more than 10 Chinese-language RCTs (not cited here, for an overview see [6])—the first ones after the small scale RCT from 1988 [146]. Since 2011, five reviews including one meta-analysis [6, 8, 69, 71, 72] covered also tiapride for the treatment of tics, while others did not even mention tiapride [40, 58]. The most recent network meta-analysis of 14 available RCTs (all conducted in China) did not find that tiapride is significantly better than placebo [6], which is in contrast to the recommendations of the AAN [3] and both Chinese [11, 12] guidelines based on RCTs. Interestingly, a recent study on therapeutic drug monitoring in 49 pediatric patients (83.7% male, mean age = 12.5 years) found a positive correlation between tiapride dose (median 6.9 mg/kg, range 0.97–19.35) and serum concentration albeit with marked inter-individual variability. The variation in dose explained 57% of the inter-patient variability in tiapride serum concentrations; age, sex, and concomitant medication did not contribute to the variability. Tics improved in 83.3% of the patients. 27.1% of the patients had mild or moderate adverse effects [147].

A meta-analysis comparing the effects of different antipsychotics in TS [6] demonstrated that the most common adverse effects in patients with TS treated with tiapride are dizziness, nausea, and dry mouth, while EPS are rare [138, 145]. However, quite rarely EPS might be observed in case of a steep drug increase in the initial phase of treatment or with irregular drug intake. Of note, tiapride can be successfully used to treat (tardive) dyskinesias due to antipsychotics [145, 148].

Noradrenergic agents

Noradrenergic agents such as clonidine and guanfacine are more commonly used in children and adolescents than in adults and mainly in those patients with a combination of ADHD and mild tics given their efficacy in treating ADHD symptoms in addition to tics.

Clonidine

For the treatment of tics, clonidine, an α-2 adrenergic agonist, has been used more commonly in America than in Europe [111] and is available as an oral and transdermal preparation. A systematic review [8] concluded that the balance of clinical benefits to harm favors the α-2 adrenergic receptor agonists clonidine and guanfacine (based on four studies with low risk of bias dating before 2011). However, the authors reported substantial heterogeneity with studies with transdermal application of clonidine being less effective compared to oral administration. The most recent meta-analysis of clonidine as treatment for TS pointed to a small standardized mean difference compared with placebo of 0.29 (95% CI [0.12–0.47]) [90]. This meta-analysis [90] indicated that the effect size of α-2 adrenergic agonist on tic reduction is much larger in children with tics plus ADHD (95% CI: 0.36–1.01) than in individuals with tics without ADHD (95% CI: − 0.06–0.36). Moreover, a prospective, open trial in 41 children and adolescents in whom previous treatment with a D2-dopamine receptor antagonist was ineffective or not well tolerated indicated a response rate of 63% after 12 weeks of treatment with a clonidine transdermal patch [149]. Unfortunately, the authors did not report effects on co-existing ADHD.

A systematic review of adverse effects of α-2 adrenergic agonists in children and adolescents with ADHD demonstrated hypotension, bradycardia, and sedation with clonidine as well as guanfacine [150]. Abrupt withdrawal of α-2 adrenergic agonists may cause rebound hypertension [151]. Therefore, blood pressure and pulse should be measured at baseline and monitored during dose adjustments and follow-up. In addition, monitoring of symptoms suggestive of cardiovascular problems (e.g., exercise intolerance, dizziness, and syncope) is recommended [152].

Guanfacine

Guanfacine, another α-2 adrenergic agonist, may reduce tics and improve ADHD symptoms in children and adolescents. However, in a recently published small-scale randomized double-blind placebo-controlled trial in children and adolescents (50% of the guanfacine, 22% of the placebo group suffered from co-existing ADHD) [153], guanfacine was not more efficacious than placebo in reducing tics. Previously, a meta-analysis of guanfacine as treatment for TS pointed to a standardized mean difference compared with placebo of 0.54 (95% CI [0.06–1.14]) [90].

The most common adverse effects of guanfacine are sedation, headache, fatigue, dizziness, irritability, upper abdominal pain, and nausea, with sedation and fatigue usually emerging within the first 2 weeks of dosing and then generally remitting [154]. Guanfacine may induce mania in children with a history or family history of bipolar disorder [155, 156]. Especially the extended release formulation of guanfacine may induce QTc prolongation [150], and therefore, patients should be monitored accordingly [3].

Other agents

Cannabis-based medicines

First reports of successful self-medication with the exocannabinoid cannabis date back to 1988 [157]. During the last years, more and more, mostly adult patients use cannabis as a self-medication and report beneficial effects [86, 158]. Indeed, there is an increasing number of case reports and small studies suggesting that cannabis-based medicines including cannabis flowers, cannabis extracts, and pure THC (dronabinol) might be effective in the treatment of tics and co-existing symptoms including ADHD. Since 2011, no new RCTs have been published. A recent meta-analysis on the two available small-scale RCTs (combined $n=41$) demonstrated no significant benefit of THC compared to placebo as treatment of TS [159]. No serious adverse reactions were reported either, with only mild adverse reactions including dizziness, tiredness, and dry mouth [160, 161].

Botulinum toxin

In addition to the use of pharmacological agents with systemic effects, there is some evidence for the efficacy of botulinum toxin injections to treat persistent well-localized motor and, sometimes, vocal tics by temporarily weakening the associated muscles, through the inhibition of acetylcholine release from peripheral motor nerve terminals. In European practice this approach is limited to older adolescents and adults in patients with insufficient response to other treatments. According to the AAN guidelines on TS [3] botulinum toxin as local application is probably more likely than placebo to reduce tics. This judgement as well as several reviews after 2011 on botulinum toxin in TS [74–85] are based on the only published randomized crossover trial of botulinum toxin injection versus placebo for the treatment of simple motor tics from 2001 conducted in 20 adolescents and adults [162]. Adverse reactions associated with botulinum toxin may include temporary soreness and mild muscle weakness including hypophonia when used in the throat region to treat disturbing vocal tics [163].

Topiramate

Topiramate is a sulfamate modified fructose diacetonide with unknown mechanisms of action. There have been no new English-language RCTs, since a 12-week randomized controlled trial of topiramate versus placebo published in 2010 that showed superior effects of topiramate compared to placebo in 29 children and adults with TS [164]. However, the authors of a recent meta-analysis [96] summarizing a total of 15 studies from China involving 1070 participants aged 2–17 years concluded that topiramate is a promising medication with good efficacy and tolerability for children with TS compared to haloperidol and tiapride.

While generally well tolerated at low doses (25–150 mg/day) it may cause a variety of adverse effects, including cognitive and language problems, aggression or mood swings, paresthesia, nausea, sweating problems, and decreased appetite [165].

Pharmacological treatment of tics in the context of co-existing psychiatric conditions

People with TS often suffer from co-existing problems, such as ADHD, OCD, mood disorders, anxiety, oppositional defiant disorder, and impulse control disorders (see Part I of this issue). The distress and burden associated with these co-existing conditions is often more significant to patients [166, 167] than the tics themselves. Although data are still limited [168], below, we present a possible approach for the treatment of co-existing psychiatric conditions in patients with TS.

Attention-deficit/hyperactivity disorder (ADHD)

ADHD is prevalent in 30–50% of referred children with TS and is strongly associated with functional impairment [166, 167]. ADHD symptoms typically improve in adolescence [169], but some adults with TS may still need continued treatment for this co-existing disorder [170]. Several pharmacological trials have assessed medication for co-existing ADHD in TS. Across studies, therapeutic doses of methylphenidate, dextroamphetamine, clonidine, guanfacine, and atomoxetine reduce ADHD symptoms as well as tics in patients with TS, probably through allowing a better self-regulatory control [99]. The α-2 agonists clonidine and guanfacine are among the agents with the most favorable efficacy-versus-adverse events ratio but effect sizes vary [8, 9, 90]. While earlier studies described that stimulants exacerbated tics or even caused first tics in some individuals [171], more recent studies demonstrated that tics do not emerge or worsen under the treatment with short-acting [172, 173] or short- and long-acting stimulants [174]; however, a transient increase may occur. On the contrary, a mild reduction of tics may occur in the treatment with methylphenidate in children with tics plus ADHD [99]. In rare cases with a persistent increase of tics after introducing a stimulant, the use of atomoxetine may be a viable alternative, which may in general have a positive effect on tics via a reduction of ADHD symptoms [3, 103]. When treating with psychostimulants, some adverse events should be taken into

consideration: sleeplessness, nervousness, headache, blood pressure raise, loss of appetite, weight loss, and gastrointestinal complaints. According to an open-label study aripiprazole results in an effective reduction of tics, but affects ADHD symptoms only moderately [175].

Obsessive–compulsive disorder (OCD)

Obsessive–compulsive behaviors are very common in people with TS, presenting frequently sensory-motor phenomena, such as urges and just-right feelings that may overlap with tics. Diagnostic criteria for OCD are met in up to 50% of people with tics [105, 176]. Trial data for OCD treatment in children (POTS II) suggest that individuals with tics respond as well to selective serotonin reuptake inhibitors (SSRIs) as those without tics and respond equally well to cognitive behavioral interventions [177] in contrast to an earlier study indicating a less favorable response to sertraline [178]. In addition, for OCD co-existing with TS, behavioral therapy approaches are the first-line treatment [3]. Small observational studies suggest that individuals without sufficient treatment response to behavioral therapy alone may benefit from an added SSRI [105]. Some fixed-dose trials of SSRIs showed that in the treatment of OCD higher doses are significantly superior to lower ones; there is, however, an expected greater adverse effect burden with higher doses of SSRIs [179]. It is worth noting that SSRIs may not only reduce OCD symptoms but also alter overall affect, anxiety, and stress sensitivity, which may lead to better self-regulation and tic suppression. However, this has not been documented in an RCT.

In treatment resistant OCD in the context of TS, antipsychotic augmentation of treatment with SSRI using aripiprazole and risperidone may be considered [180]; the subgroup of patients with OCD and co-existing tics had a particularly beneficial response to treatment with antipsychotic augmentation in a meta-analysis [179]. However, it is important to keep in mind the limited evidence base and the need for drug safety monitoring, as pointed out in an observational study including children with tic-related OCD [180] as well as a meta-analysis including adults with OCD (without tics) [181].

Other co-existing psychiatric conditions

In addition to ADHD and OCD, people with TS are at risk of developing depression, anxiety disorders, oppositional defiant disorder, rage attacks, and mood disorders [176]. Co-existing mood disorders are more often seen in adolescents and adults than in children and in those with greater tic severity [3]. It is worth noting that there is an increased risk of suicidal ideation, suicide attempts, and suicide in people with TS, also when statistically controlling for other co-existing psychiatric conditions [182]. Unfortunately, there are no treatment studies to guide the clinician in treating these co-existing problems.

Guanfacine and clonidine can be effective in individuals with co-existing impulse control disorder [90]. Aripiprazole and risperidone are useful for co-existing irritability and aggressive behaviors [183–186].

Tics and stereotyped movements are frequent in Autism Spectrum Disorder, and a clear diagnostic distinction between them may be challenging to establish [28, 106]. Treatment with risperidone or fluoxetine may be considered in cases with stereotypies that are debilitating and involving harm and injury to self and others [187].

Clinical recommendations for the pharmacological treatment of TS

Decisions about treatment of TS should be based on a thorough and broad diagnostic process (see Part I of this issue). Behavioral therapy approaches are recommended as first line treatment, based on assumed better tolerability of behavioral therapy, because behavioral approaches might strengthen the patients' self-regulatory control [3, 188] (see Part V of this issue). However, these are not always locally accessible (a major factor in many countries) or feasible because of low introspective ability in young age or low IQ, or due to low motivation or ability to invest time and effort required for practicing in behavioral therapy. For individuals with clear impairments associated with their tics or with a preference for pharmacotherapy, after psychoeducation pharmacologic interventions may be considered alone or in addition to behavioral therapy. This concerns especially situations, where tics impair quality of life and cause subjective discomfort (e.g., pain or injury) or when tics result in sustained social problems (e.g., social isolation or bullying) or cause functional interference (e.g., impairment of academic achievements) [111]. In addition, pharmacological treatment acts faster, because prescription, dispensing, and intake of first dose are easier than planning and commencing behavioral therapy. Moreover, first treatment effects are often seen within a few days, while after behavioral therapy first beneficial effects in most cases cannot be observed until after a few weeks. Therefore, pharmacotherapy may be preferred in situations, where a rapid tic reduction is urgently required.

The waxing and waning course (including its time course) of the tics in each individual should be taken into account when deciding on starting therapy and when evaluating treatment effects.

Independently from the individual factors that result in the decision to start pharmacological treatment of tics it is important to inform patients and their parents about what can be achieved by this kind of treatment to avoid too high expectations. On average, a tic reduction of 50% can

be expected. However, some patients report a reduction of 90%, while others feel no or only minimal improvement.

The decision to propose a treatment with a specific agent is an individual choice made by the clinician, in collaboration with the patient and family and depends on the patient's needs, preferences, and priorities as well as on the physician's preferences, experience, and local regulatory requirements.

During the last decades, several agents have been suggested and used as rational medication for the treatment of tics. Based on evidence from RCTs and on clinical experience aripiprazole, tiapride, and risperidone for TS as well as clonidine and guanfacine for TS and co-existing ADHD are the best established options, all on the basis of off-label use. In general, we recommend a "start low, go slow" drug up-titration, meaning that the therapy should be initiated with the lowest dose possible and gradually increased. It is important to bear in mind that the antipsychotic dosages normally used for the treatment of tics are considerably lower than those used to treat psychotic disorders.

Depending on its individual receptor binding profile, each agent bears the risk of specific adverse effects. Therefore, not only effectiveness but also potential adverse effects of each agent should be taken into consideration when deciding about the most suitable agent for a patient with TS. Most pharmacological treatments discussed in these guidelines have well known adverse effects, including weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on heart rate, blood pressure, and electrocardiograms. Therefore, careful monitoring of adverse events is recommended (see Table 2). In case of treatment discontinuation, gradual tapering off antipsychotic medications is recommended to avoid withdrawal dyskinesias [3].

An important aspect when choosing an agent for a patient is also the presence of co-existing conditions. Often, the co-existence of ADHD or OCD, as well as mood, anxiety, or impulse control disorders may be more disturbing to the patient than the tics [167] and may thus have important implications for the choice of medication. Evidence for those choices is still limited, but this differentiation already presents an important step towards an individualized approach to medication in TS.

While the evidence-based practice recommendations of the AAN did not present a hierarchical recommendation what agent should be given first, the ESSTS survey indicates that aripiprazole is now the most commonly used agent for the pharmacological treatment of TS for both age groups (children and adolescents, adults). This may be the result of several factors, one being the unique pharmacological profile as a dopamine partial agonist [189], but also the availability of several RCTs with sufficient sample sizes that document a favorable benefit-risk ratio, predominantly being the result of its positive profile of adverse effects [69, 70, 72]. Positron emission tomography studies demonstrated that the clinical effect of an antipsychotic emerges when more than 65% of striatal dopamine D2 receptors are blocked, and EPSs become apparent when the receptor blockade exceeds 80% [190]. Thus, in the ideal antipsychotic therapy (antipsychotic efficacy without EPSs), about 70% of striatal dopamine D2 receptors are blocked. When tight antipsychotics bind 70% of D2 receptors, the remaining 30% are available for endogenous dopamine to bind. This means that dopaminergic transmission is reduced to 30%, and both tonic/phasic components are suppressed equally. In one study, aripiprazole was effective at a dose of up to 20 mg, where 10% or fewer D2 receptors were available for endogenous dopamine to bind; however, EPSs did not appear, because aripiprazole exerted a partial dopaminergic agonistic activity [191].

Tiapride, the second most commonly prescribed agent in children and adolescents with tics, especially in Germany, has a similar working mechanism as aripiprazole, showing a maximum of 80% of dopamine receptor occupation even in the presence of excess tiapride concentrations [145]. Interestingly, for two of the most commonly used agents according to the ESSTS survey there is evidence from pharmacodynamic studies explaining their low (aripiprazole) or very low (tiapride) potential for EPS compared to haloperidol [69, 70, 138, 145].

Another recommended antipsychotic agent, risperidone, actually has a good evidence base, but is associated with weight gain and metabolic adverse effects.

The European survey documented that noradrenergic agents are the third most given agents regarding both age groups together. Importantly, noradrenergic agents have a low effectiveness in patients with tics only, but this substantially increases in patients (particularly children and adolescents) with the combination of tics and ADHD, both for reducing tics and symptoms of ADHD [8, 90]. Therefore, we recommend noradrenergic agents as first line treatment of mild to moderate tics in patients with co-existing ADHD, but less in those without co-existing ADHD as there they have only minimal benefits. However, in some patients with mild tics only, noradrenergic agents may be more acceptable than antipsychotics, based on more favorable adverse effects.

In treatment resistant cases, treatment with agents with sometimes a still limited evidence base and less frequently prescribed by ESSTS experts might be considered. Reasonable choices include antipsychotics including haloperidol, pimozide, quetiapine, sulpiride, and amisulpiride as well as cannabis-based medicines, topiramate, and botulinum toxin injections.

Haloperidol is still relatively often used in adults with TS, but rarely mentioned by any ESSTS expert as treatment option for children and adolescents. Its declined use can be explained by its unfavorable adverse effect profile compared to other antipsychotics, even though haloperidol is the only officially licensed substance for TS and tics in Europe, and has a long tradition and established efficacy in the treatment of TS, with relatively low costs.

Table 2 Most common medications for Tourette syndrome and other chronic tic disorders

Medication	Indication	Start dosage (mg)	Therapeutic range per day (mg)	Effect size*	Confidence in the quality of the evidence**	Very common adverse events (> 10%)***	Physical and laboratory Examinations at the start and at follow-ups
α-2 adrenergic agonists							
Clonidine	ADHD/TS	0.025	0.025–0.3 (titrated according to BP and HR)	0.29 (0.12–0.47) [90]	Moderate	Dizziness, orthostatic hypotension, dry mouth	Blood pressure, ECG
First generation antipsychotics							
Haloperidol	TS	0.25–0.5	0.25–3.0	3.20 (0.14–6.52) [6]	Moderate	Agitation, insomnia, EPS, hyperkinesia, headache	ECG, weight
Pimozide	TS	0.5–1.0	1.0–4.0	0.42 (−0.07–0.90) [6]	Low	Dizziness, somnolence, hyperhidrosis, nocturia	ECG, weight
Newer antipsychotics							
Aripiprazole	TS	2.50	2.5–30	4.74 (1.06–8.67) [6]	Moderate	Somnolence, sedation	Weight, blood lipids, and glucose
Risperidone	TS/DBD	0.25	0.25–3.0	3.47 (0.37–6.87) [6]	Moderate	Insomnia, sedation/somnolence, parkinsonism, headache	Weight, prolactin, blood lipids, and glucose
Benzamides							
Tiapride	TS	50–100 (2 mg/kg)	100–600 (2–10 mg/kg)	0.47 (−3.89–5.06) [6]	Moderate	Hyperprolactinemia*, sleepiness, insomnia, agitation, impassivity, vertigo, headache	ECG, weight, prolactin
Others							
Botulinum toxin	TS	Vocal tics: 1–2.5 U Motor tics: 50–75 U	1–2.5 75–250	1.27 (0.51–2.03) [4]	Moderate	Weakness of the injected muscles	

DBD disruptive behavior disorder; *OCB* obsessive–compulsive behavior; *TS* Tourette syndrome; *ADHD* attention-deficit/hyperactivity disorder; *BMI* body mass index; *EP*S extrapyramidal symptoms; *BP* Blood pressure; *HR* heart rate; *ECG* electrocardiogram

Information on the adverse effects stems from the official Summaries of product characteristics, if no very common Adverse Events (> 10%), *standardized mean difference compared with placebo (including 95% confidence interval; positive number pointing to efficacy) according to the most recent meta-analysis (for botulinum toxin based on a single study), as referenced ** based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) as reported by AAN [4] ***common Adverse Events (< 10% and > 1%) are provided

Current limitations and future directions

In the light of the limited existing evidence several questions remain unanswered: most importantly, the effectiveness of combinations of behavioral therapy with pharmacological treatment and of different agents needs further trials. Studies directly comparing different agents or combinations of agents in TS are rare, and there is currently only one study [192] available that compared pharmacological treatment with behavior therapy, yielding equal effects within a study period of 10 weeks. Moreover, the study periods of published trials on pharmacological treatment of TS were quite short, e.g., in view of the natural waxing and waning course of tics in TS. In addition, research should be conducted on treatment sequencing and decision-making and for whom particular sequences of treatment are most effective [3].

Another area in need of further evidence is the treatment of patients with co-existing conditions. Moreover, questions around how to deal with treatment refractoriness remain unanswered [193]. The risk of adverse events when using specific agents needs further exploration, e.g., sudden death due to QTc prolongation [116], hyperprolactinemia and its consequences [109], and weight gain [128]. In addition, the questions of optimal treatment duration, as well as long-term outcome after discontinuation of a pharmacological treatment of tics remain unanswered. These important points for the pharmacotherapy of TS are still open to discussion due to a non-existent or too small base of evidence and are important areas for future research. Unfortunately, the number of new agents that might be effective as treatment of TS is limited. Perhaps most promising are the Chinese herbal medicine products 5-ling granule and Ningdong granule, which were classified as compounds showing moderate confidence in evidence of treatment effects according to the AAN guidelines, based on well-powered RCTs conducted in China. However, these products are currently not available to clinicians on the European market. One final future step to improve pharmacological treatment of TS would be precision medicine as well as personalized medicine [194] by prior genetic testing or the use of other neurobiological markers [195]. This approach, however, is still an aspiration for neuropsychiatric disorders, such as TS.

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Declarations

Conflict of interest VR has received payment for consulting and writing activities from Lilly, Novartis, and Shire Pharmaceuticals, lecture honoraria from Lilly, Novartis, Shire Pharmaceuticals, and Medice Pharma, and support for research from Shire Pharmaceuticals and Novartis. He has carried out clinical trials in cooperation with the Novartis, Shire, Servier and Otsuka companies. KMV has received financial or material research support from the EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), the German Research Foundation (DFG: GZ MU 1527/3-1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), the Tourette Gesellschaft Deutschland e.V., the Else-Kröner-Fresenius-Stiftung, and Abide Therapeutics, Almirall Hermal GmbH, GW pharmaceuticals, Lundbeck, Syneos Health, and Therapix Biosciences Ltd. She has received consultant's honoraria from Abide Therapeutics, Allmiral, Boehringer Ingelheim International GmbH, Bionorica Ethics GmbH, CannaMedical Pharma GmbH, Canopy Grouth, Columbia Care, CTC Communications Corp., Eurox Deutschland GmbH, Global Praxis Group Limited, IMC Germany, Lundbeck, Resalo Vertrieb GmbH, Sanity Group, STADAPHARM GmbH, Synendos Therapeutics AG, and Tilray. She is/was a consultant or advisory board member for Abide Therapeutics, The Academy of Medical Cannabis Limited, Alirio, Aphria Deutschland GmbH, CannaMedical Pharma GmbH, Bionorica Ethics GmbH, CannaXan GmbH, Canopy Growth, Columbia Care, CTC Communications Corp., IMC Germany, Leafly Deutschland GmbH, Lundbeck, Nuvelution TS Pharma Inc., Resalo Vertrieb GmbH, Sanity Group, Syqe Medical Ltd., Therapix Biosciences Ltd., Tilray, and Wayland Group. She has received speaker's fees from Aphria Deutschland GmbH, Cogitando GmbH, Emalex, Eurox Deutschland GmbH, Ever pharma GmbH, PR Berater, Spectrum Therapeutics GmbH, Tilray, and Wayland Group. She has received royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, Elsevier, and Kohlhammer. She served as a Guest editor for Frontiers in Neurology on the research topic "The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects", and is Associate editor for "Cannabis and Cannabinoid Research", Editorial Board Member for "Medical Cannabis and Cannabinoids" and "MDPI-Reports", and scientific board member for "Zeitschrift für Allgemeinmedizin". CG is supported by VolkswagenStiftung (Freigeist Fellowship) and served ad hoc as advisory board for Lundbeck. AC is author of the book "Pharmacological Treatment of Tics". Cambridge University Press, 2020. PJH has received a payment as member of an advisory board meeting of Shire Pharmaceuticals and has carried out a clinical trial in cooperation with Servier. All other authors declare that they have no conflict of interests.

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REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part IV: deep brain stimulation

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Abstract
In 2011 the European Society for the Study of Tourette Syndrome (ESSTS) published its first European clinical guidelines for the treatment of Tourette Syndrome (TS) with part IV on deep brain stimulation (DBS). Here, we present a revised version of these guidelines with updated recommendations based on the current literature covering the last decade as well as a survey among ESSTS experts. Currently, data from the International Tourette DBS Registry and Database, two meta-analyses, and eight randomized controlled trials (RCTs) are available. Interpretation of outcomes is limited by small sample sizes and short follow-up periods. Compared to open uncontrolled case studies, RCTs report less favorable outcomes with conflicting results. This could be related to several different aspects including methodological issues, but also substantial placebo effects. These guidelines, therefore, not only present currently available data from open and controlled studies, but also include expert knowledge. Although the overall database has increased in size since 2011, definite conclusions regarding the efficacy and tolerability of DBS in TS are still open to debate. Therefore, we continue to consider DBS for TS as an experimental treatment that should be used only in carefully selected, severely affected and otherwise treatment-resistant patients.

Keywords Tics · Tourette syndrome · Deep brain stimulation · Treatment · Guidelines · European Society for the Study of Tourette Syndrome (ESSTS)

Introduction

Tourette syndrome (TS) is a chronic motor and vocal tic disorder. The prevalence of TS in general population is estimated at 0.3–1% [1–3]. After the onset, usually at the age of about 4–6 years, tics tend to have a waxing and waning course over the years and generally reach a maximum severity around 12 years [4]. In the vast majority of patients, thereafter tics decrease during adolescence or early adulthood and overall have a favorable prognosis. In those patients suffering from disabling tics, behavioral and/or pharmacotherapy is recommended as first line treatments [5–8].

A minority of patients experiences a persistent course and does not benefit from well-established treatments and/or experience serious side effects such as significant weight gain, hyperprolactinemia, somnolence and tiredness [9]. To date, there is no generally established definition available for "treatment refractoriness" and exact number of "treatment-refractory" patients is unknown [10–12]. However, there is broad agreement that various types of treatments in adequate doses, frequency, and duration should have been used before classifying a patient as otherwise "treatment-refractory". Surgical treatment with deep brain stimulation (DBS) should be taken into consideration only in patients with severe and otherwise treatment-refractory tics. In most of these severely affected patients, psychiatric comorbidity such as attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive symptoms (OCS) or disorder (OCD), depression, anxiety, and self-injurious behavior (SIB) is present that often

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impairs patients' quality of life more than the tics [13–16]. Thus, before considering DBS for tics in TS, the best possible treatment of psychiatric symptoms—notably obsessions, compulsions and depression—should have been carried out [17, 18].

In TS, ablative surgery with prefrontal lobotomy was first performed in 1955 [19]. The first surgical treatment using the thalamus as a target was undertaken in 1970 by Hassler and Dieckmann [20], who performed thalamotomy in the centromedial–parafascicular complex (CM–Pf) and nucleus ventro-oralis internus (Voi) in three patients, which resulted in a tic reduction of 70–100% [21]. Subsequently, Babel et al. [22] reported tic reduction in 14 of 17 patients after ventriculography-based stereotactic zona incerta (ZI) and ventrolateral/lamella medialis thalamotomy (VL/LM). However, in a large number of patients postoperative complications occurred including (transient or permanent) cerebellar ataxia, dysarthria, dystonia, and hemiballism. Finally, in 1999 [23] thalamic deep brain stimulation (DBS) was performed for the first time in three otherwise treatment-refractory adult patients with TS. Subsequently, several other targets have been suggested.

In 2011, the European Society for the Study of Tourette Syndrome (ESSTS) published its first European clinical guidelines on the treatment of TS with part IV on DBS [18]. Here, we provide our updated guidelines with recommendations for the clinical practice of DBS in TS based not only on the evidence obtained over the past decade, but also on expert knowledge including results from a survey among a large number of ESSTS experts.

Methods

For the current version of part IV of the European clinical guidelines, a literature search was carried out. The aim was to identify relevant research on efficacy and safety of DBS for TS published between January 2011 and August 2021. Our systematic approach was based on the search in PubMed, Ovid, Web of Science, Embase, and APA Psych Info conducted on March 2020 and again on August 27, 2021. We searched for articles reporting about DBS in TS using the search terms "tics" AND/OR "Tourette" AND/OR "deep brain stimulation" AND/OR "DBS". Reviews and meta-analyses in the area were further searched for relevant citations. In addition, the reference lists of the articles identified were reviewed for additional studies. In addition to the studies identified through systematic review, to make the publication list as comprehensive as possible, studies still in press and not officially published were added by the authors (i.e. through precedent knowledge about relevant publications). The methodology of the ESSTS survey is presented in a summary paper in the current issue of this journal [24].

Review of the literature (based on search of studies on DBS between 1970 and August 2021)

Preliminary note: The available evidence for DBS in TS is still very limited. Available evidence is based on few small randomized controlled trials (RCTs), open uncontrolled case reports and case series, registries, and meta-analyses. It is important to note that data largely overlap and results from one single patient may be included in more than one report. To give the best possible overview and comparability, we report data depending on the study design. For more detailed results we refer to the original publications.

When the first version of the ESSTS DBS guidelines was published in 2011 [18], only 3 RCTs were available, each including 1 to 5 patients [25–27] with altogether nine patients. In addition, open and uncontrolled reports covering a total of 63 patients were published, which reported beneficial outcomes with moderate to marked tic improvement in the vast majority of patients (59/63 patients). Since this review, five subsequent RCTs have been published, resulting in a total of 62 patients in all RCTs. Thus, until today there is still only a total of eight RCTs available including a maximum of 17 patients [25–32]. A summary of these studies is presented in Table 1. In addition, data from the International Deep Brain Stimulation Database and Registry including 185 patients (published in 2018 [33]), one retrospective analysis on long-term follow-up in 110 patients (published in 2019 [34]), and two meta-analyses (published in 2016 and 2018) including 58 [35] and 156 [36] patients were published. In addition, data from several further open uncontrolled studies and case series were published including 2 to 123 subjects as well as more than 100 single case reports (for summary see Table 2).

Randomized controlled trials

To date, since 1999, 8 RCTs examining efficacy and safety of DBS in TS have been published with a total of 62 patients (for further details including target, treatment duration, effects on tics and comorbidities see Table 1). However, results are still limited by small sample sizes (ranging from 1 to 17 patients). The first trial by Houeto et al. [25] included only one patient who was treated with bilateral high frequency stimulation of the centre median nucleus/parafascicular complex (CM–Pf), the internal

Table 1 RCTs using DBS in TS (in chronological order)

Authors	Numbers of patients*	Target	Duration (months)		Mean tic improvement (according to YGTSS)**	
			Double-blind controlled study part	Open uncontrolled study part	Double-blind controlled study part	Open uncontrolled study part
Houeto et al. [25]	1/1	CM-Pf, internal part of the GPi	11	24	Tic reduction of 59–70% depending on target Mean tic reduction of 41.25 according to YGTSS-TTS	"Improvement" (no data shown)
Maciunas et al. [26]	5/5	Bilateral thalamic stimulation	1	3	Mean tic reduction of 2.4 according to YGTSS-TTS	Improvement in 3/5 patients Mean tic reduction of 9.0 according to the YGTSS-TTS at the 3-Month follow-up Mean overall reduction of 38.8 (44%) according to YGTSS-GS at 3 months compared with the preoperative score
Welter et al. [27]	3/3	GPi and thalamic stimulation	8	20–60	Tic improvement ranging from 30 to 96% according to YGTSS-TTS	Tic improvement ranging from 74 to 82% according to YGTSS-TTS
Ackermans et al. [31]	6/6	Thalamic stimulation	6	12	Significant improvement ($p=0.046$) of 37% according to YGTSS-TTS Mean YGTSS-TTS improvement of 15.5	Significant improvement ($p=0.028$) of 49% according to YGTSS-TTS Mean YGTSS-TTS improvement of 20.7
Kefalopoulou et al. [30]	13/15	GPi	6	8–36	Significant tic improvement according to YGTSS-TTS ($p=0.048$) Mean improvement in YGTSS-TTS of 12.4	Significant improvement according to YGTSS-TTS ($p<0.0001$) Mean improvement in YGTSS-TTS of 36.3
Welter et al. [29]	16/16	GPi	3	6	No significant improvement ($p=0.39$) Mean reduction of 1.2 according to YGTSS-TTS	Significant improvement (no p shown) Mean reduction of 30.3 according to YGTSS-TTS
Müller-Vahl et al. [28]	10/10	GPi vs thalamic stimulation	9	6–89.9	Significant tic reduction at group level, after GPi—but not thalamic—DBS compared to baseline No effects on premonitory urges and psychiatric comorbidities Inconsistent or negative findings when comparing targets directly	At group level, no improvement of tics, comorbidities, and quality of life Single patients benefitted continuously from thalamic DBS At last follow-up 89.9 months (mean) after surgery, 50% of patients had discontinued DBS

Table 1 (continued)

Authors	Numbers of patients*	Target	Duration (months)		Mean tic improvement (according to YGTSS)**	
			Double-blind controlled study part	Open uncontrolled study part	Double-blind controlled study part	Open uncontrolled study part
Baldermann et al. [32]	8/8	Thalamic stimulation	48 h of ON followed by 48 h sham stimulation at 6 and 12 months	12	Significant tic reduction according YGTSS ($p = 0.001$) YGTSS tic scores were significantly decreased with active stimulation by 26% compared to discontinued stimulation after 6 months and by 44% after 12 months	YGTSS tic scores decreased significantly from baseline to 6 months ($p < 0.001$) and twelve months ($p = 0.001$) but not from 6 months to 12 months ($p = 1.0$)

RCTs randomized controlled trials, *YGTSS* Yale Global Tics Severity Scale, *YGTSS-TTS* Total Tic Score of the YGTSS, *DBS* Deep Brain Stimulation, *TS* Tourette syndrome, *GPi* Globus pallidus internus, *CM-Pf* the centromedian–parafascicular nuclei complex of thalamus

*The first number refers to the number of patients included in the double-blind controlled study phase, the second number refers to those in the open uncontrolled study phase **when no mean improvement according to YGTSS was shown, we present the descriptive results

part of the globus pallidus (GPi), or both. Stimulation of either target resulted in tic improvement of 70%, markedly ameliorated coprolalia, and eliminated SIB. In another double-blind crossover trial of bilateral thalamic DBS in five adults with TS [26] a statistically significant ($p < 0.03$) reduction in the modified Rush Video-Based Rating Scale was identified and motor and vocal tics significantly improved according to the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS). Welter et al. [27] included three patients with severe, medically refractory TS who received bilateral stimulation in the CM-Pf and the GPi. Both interventions resulted in significant improvement of tics ranging from 30 to 96%. The two largest RCTs (both using GPi DBS) included 15 [30] and 17 [29] patients respectively, and demonstrated overall tic improvement during the blinded study phase of 15.3% ($p = 0.048$) on the YGTSS-TTS in one study [29], but no improvement in the other (median tic reduction of 1.1%, $p = 0.39$) [30]. However, in both studies a significant improvement was reported at the end of the open-label phase after several months (6–48 months) with a tic reduction of 40.1% and 69.5%, respectively [29, 30, 95]. In the third largest RCT [28] (comparing efficacy and safety of bilateral DBS of CM-Voi versus posteroventral lateral pvl) Gpi versus sham stimulation), 10 patients were included and GPi DBS ($p = 0.05$)—but not thalamic DBS ($p = 0.18$)—resulted in a significant tic reduction compared to baseline, but had no effect on premonitory urges and psychiatric comorbidities. Direct comparisons of both targets to sham stimulation resulted in inconsistent or negative findings. During follow-up, at group level, no improvement of tics, comorbidities, and quality of life was demonstrated, while single patients benefitted continuously from thalamic DBS. In another RCT (using the CM-Voi of the thalamus), six patients were included and a significant tic reduction of 37% was described in the blinded phase ($p = 0.046$) and of 49% ($p = 0.028$) after one year of open label phase [31]. Finally, in 2021 Baldermann et al. [32] published results of their RCT in which eight patients with TS were included. The authors investigated the course of tic severity, comorbidities and quality of life during thalamic stimulation (Cm-Voi). The patients were assessed at baseline, after 6 months and 12 months after the surgery in the open label phase. Double-blind phase consisted of sham-controlled periods that took place at 6 and 12 months after the implantation and the patients received 48 h ongoing DBS (ON) followed by 48 h with sham stimulation (OFF) or vice versa in a crossover design. In double blind phase, significant tic reduction according to YGTSS ($p = 0.001$) occurred. In particular, the YGTSS tic scores were significantly decreased with active stimulation by 26% compared to discontinued stimulation after 6 months and by 44% after 12 months. In open label phase YGTSS tic

Table 2 Published case reports and other open uncontrolled studies using DBS in patients with TS

Single case reports		
N of studies	*N* (patients)	References
35	1	[23, 37–70]
Case series		
N of studies	*N* of patients (range)	References
25	2–55	[37, 71, 71–94]
Open uncontrolled studies		
N of studies	*N* of patients (range)	References
28	1–123	[34, 95, 95–122]

DBS deep brain stimulation, *TS* Tourette syndrome

scores decreased significantly from baseline to 6 months ($p < 0.001$) and 12 months ($p = 0.001$) but not from 6 to 12 months ($p = 1.0$).

With respect to psychiatric comorbidity, only limited information is available. In 6 of 8 RCTs [25–27, 29, 30, 32], the effects of DBS (at different targets) on psychiatric symptoms are reported suggesting that DBS may also have beneficial effects on depression and/or anxiety. Effects on OCS and OCD varied, while there seems to be no effect on ADHD (for details see Table 3). It can be speculated that beneficial effects on depression and anxiety might be—at least in part—secondary due to improved tics. Furthermore, it has been speculated that assessment scales used for psychiatric symptoms might be less appropriate for use in patients with TS [31].

The International Deep Brain Stimulation Database and Registry

In 2018, data from a large international cohort were published based on the International Deep Brain Stimulation Database and Registry [33]. At the time, this registry included 185 patients with otherwise treatment-refractory TS, who underwent DBS implantation between 2012 and December 2016 at 31 institutions in 10 different countries (exact details about methodology of the data collection and analysis can be consulted in the paper by Martinez-Ramirez et al. [33]). The authors mainly focused on the efficacy of DBS in reducing tics at 6 and 12 months after DBS implantation as measured using the YGTSS-TTS) and the number and profile of adverse events (AEs) related to both surgery (such as infections and hemorrhage) and stimulation (such as paresthesias, bradykinesia, depression, and dystonia). In addition, sub-analyses were performed with respect to the target used [33]. The study reports that: (i) on average, DBS resulted in a tic improvement of 45.1% according to the YGTSS-TTS, (ii) the overall rate of AEs was high (35.4%) and most of the AEs were stimulation-related (30.8%), whereas 3.8% were surgery-related and only 1.3% were device-related, (iii) the most frequently used target was the centro-median thalamic region (57.1%, 93/163 patients), followed by the anteromedial part of the GPi (25.2%, 41/163 patients), the postero-ventrolateral part of the GPi (15.3%, 25/163 patients), and the anterior limb of the internal capsule (ALIC) (2.5%, 4/163 patients). Detailed data on the AEs are shown in subsequent paragraphs. Data obtained from other stimulation targets were not given. There was no evidence for superiority of a particular target [33]. Data from the same registry were complemented by a follow-up analysis published in 2019 [34]. Details are presented in the "Retrospective analysis on long-term follow-up" section.

Meta-analyses

To date, two meta-analyses have been published investigating efficacy and safety of DBS in adults (published in 2016) [36] and in children and youth [35] (published in 2018). Baldermann et al. [36] included 57 studies (both controlled and uncontrolled) with a total of 156 adult patients. Based on these data, DBS resulted in an average improvement of tics of 52.7% on the YGTSS-TTS (IQR = 40.74, $p < 0.001$). Analysis of data from controlled studies only (four studies with a total of 27 patients [25, 26, 30, 31]) favored "on stimulation" versus "sham stimulation" with a standardized mean difference of 0.96 (95% CI 0.36–1.56).

With respect to the target (thalamus, posteroventrolateral part of the GPi, anteromedial part of the GPi, ALIC, and nucleus accumbens (NA), no significant differences were found in tic reduction, when analyzing data of all 57 studies together [36]. However, further analyses suggested that different patient groups benefitted differently from stimulation at different targets. In particular, thalamic stimulation was more effective when tics were less severe. In contrast, YGTSS-TTS after GPi DBS correlated positively with preoperative impairment score of the YGTSS, but not with the tic specific score (YGTSS-TTS). Regarding psychiatric comorbidities, Baldermann et al. [36] found a median reduction of OCD of 31.3% on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Subgroup analysis did not show a difference in reduction of OCD symptoms between targets ($p = 0.812$). Moreover, there was a median improvement of mood of 38.9% (measured with the Beck Depression Inventory (BDI)). Again, subgroup analysis did not show differences between targets ($p = 0.692$).

In the second meta-analysis data on efficacy and safety of DBS specifically in children and youth (aged 12–21 years, mean age 17.9 ± 2.7) is summarized based on 21 studies including 58 cases. The authors report an average tic improvement of $57.5\% \pm 24.6\%$ [35]. Comorbid depression

Table 3 Effect of DBS on psychiatric comorbidities in TS

Authors	Study type	*N**	Comorbidities assessed	Results of the double blind phase	Results of the open label phase
Houeto et al. [25]	RCT	1/1	Depression, anxiety, impulsivity	Range of change of − 8 to 60% in depression (MADRS) Range of change of 0 to + 110% in anxiety (BAI) Range of change of –14 to 55% in Impulsivity (BIS) Reduction of self-injurious behavior	Improvement of self-injurious behavior
Maciunas et al. [26]	RCT	5/5	Depression, anxiety, OCD	Trends towards improvements in depression (BDI, HAM-D), OCD (Y-BOCS), and anxiety (HAM-A)	A non-significant trend for decreased verbal fluency, memory, and sustained attention and reaction time at the 3-month follow-up compared with levels at the preoperative assessment BDI-2,HAM-D, HAM-A, and Y-BOCS showed a trend toward improved mood, reduced anxiety, and fewer obsessions and compulsions
Welter et al. [27]	RCT	3/3	Depression, anxiety, OCD	Improvement during both pallidal and thalamic stimulation in 2/2 patient with depression (MADRS) Improvement of anxiety in 2/2 patients with anxiety (BAI) No change in OCD (0/0) (no scale used)	A dramatic reduction in self-injurious behavior and impulsiveness
Ackermans et al. [31]	RCT	6/6	Depression, anxiety, OCD, ADHD, self-injurious behaviors	No effect on any comorbidities (Y-BOCS, CAARS, BAI, BDI)	No effect on any comorbidities (Y-BOCS, CAARS, BAI, BDI)
Kefalopoulou et al. [30]	RCT	13/15	Depression, anxiety, OCD	No improvement of depression ($p = 0.127$, BDI) No improvement of anxiety ($p = 0.352$, STAI) No improvement of OCD ($p = 0.979$, Y-BOCS)	Significant improvement of mood (BDI) Modest, non-significant effects in OCD (Y-BOCS) and anxiety (STAI)
Welter et al. [29]	RCT	16/16	Depression, anxiety, OCD	No improvement of depression ($p = 0.25$, MADRS and $p = 0.08$, HAM-D) No improvement of OCD ($p = 0.25$, Y-BOCS) No improvement of anxiety ($p = 0.91$, BAS)	Significant changes between inclusion and the end of the open-label period in anxiety (MADRS, HADS) No significant changes in depression (BAS, HADS) and OCD (Y-BOCS)
Müller-Vahl et al. [28]	RCT	10/10	OCD, ADHD, depression, anxiety	No effect on any comorbidities (Y-BOCS, CAARS, BAI, BDI)	OCD completely remitted (Y-BOCS) None of the patients exhibited a reduction in CAARS values of ≥ 30% at any follow-up visit Due to incompliance, only incomplete data were available without convincing evidence suggesting changes in mood No changes in anxiety (STAI)
Baldermann et al. [32]	RCT	8/8	Depression, OCD, anxiety, ADHD	Not assessed	Significant improvement of OCD, depression and anxiety
Baldermann et al. [36]**	M	156	Depression, OCD	Median reduction of 31.25% in OCD (Y-BOCS) Median reduction of 38.89% in depression (BDI)	Median reduction of 31.25% in OCD (Y-BOCS) Median reduction of 38.89% in depression (BDI)

Table 3 (continued)

Authors	Study type	*N**	Comorbidities assessed	Results of the double blind phase	Results of the open label phase
Coulombe et al. [35]**	M	58	Depression, anxiety, OCD	Range of change of − 75 to + 100% in OCD (Y-BOCS) Range of change of − 2.6 to + 58% in anxiety (STAI) Range of change of − 80 to + 100% in depression (HAM-D)	Range of change of − 75 to + 100% in OCD (Y-BOCS) Range of change of − 2.6 to + 58% in anxiety (STAI) Range of change of − 80 to + 100% in depression (HAM-D)

Included are all RCTs and meta-analyses giving respect data

DBS deep brain stimulation, *TS* Tourette syndrome, *M* meta-analysis, *RCT* randomized controlled trial, *OCD* obsessive–compulsive disorder, *ADHD* attention deficit hyperactivity disorder, *Y-BOCS* Yale-Brown Obsessive–Compulsive Scale, *BDI* Beck Depression Inventory, *STAI* The *State-Trait Anxiety Inventory*, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *MADRS* the Montgomery–Åsberg Depression Rating Scale, *BAI* Beck Anxiety Inventory, *BIS* the Barratt Impulsiveness Scale, *CAARS* the Conners' Adult ADHD Rating Scales

*The first number refers to the number of patients, included in the double- blind controlled study phase, the second number refers to those in the open uncontrolled study phase, **this study did not distinguish between RCT and open studies. No data are included from the International Tourette DBS Registry and Database, since no results on comorbidities were given

correlated negatively with outcome ($p < 0.05$). In patients with less severe tics greater improvements were evident following thalamic stimulation. More than one-quarter ($n = 16$, 27.6%) of participants experienced AEs, mostly mild in severity. For further details please consult the subsequent section dedicated to AEs. The authors' interpretation of the data is that in carefully selected children and youth with treatment refractory TS, DBS is an effective treatment for tics with a moderate safety profile. In none of the meta-analyses, any predictors were found that allow a prognosis of outcome after DBS.

Retrospective analysis on long-term follow-up

In 2019, Johnson et al. [34] published results of the largest retrospective analysis so far based on the International Deep Brain Stimulation Database and Registry involving 13 sites from North America (39 patients), Europe (63 patients) and Asia (21 patients). They assessed the effects of DBS in the long-term follow-up (up to 96 months) of 110 patients with TS, who were implanted in the CM-Pf and the CM/Voi of the thalamus ($n = 51$), the GPi ($n = 47$), the NA/ALIC ($n = 4$) or combinations of these targets ($n = 8$). Similarly to Baldermann et al.'s meta-analysis [36], the authors report that both tics and OCS significantly improved over time ($p < 0.01$). The median time to reach a 40% improvement of tics was 13 months. However, no significant differences were found between different brain targets ($p > 0.05$). Just recently, Kimura et al. [96] reported about findings from clinical practice and outcome of DBS in TS in Japan. They included 25 patients with refractory TS treated with thalamic CM-Pf DBS. Compared to baseline, tic severity measured by YGTSS-TTS improved by 45.2% at 1 year, and by 56.6% at last follow-up 3 years after surgery. Besides reduction of both motor and vocal tics, an improvement of quality of life was observed.

Target selection

To date it is not clear which target should be selected in TS. The most often used targets are different parts of the thalamus (CM–Pf and CM/Voi) and the postero-ventrolateral and the anteromedial part of the GPi. However, several other targets have been suggested for the management of tics (and comorbidities) in TS including the NA, the ALIC, the globus pallidus externus (GPe), the subthalamic nucleus (STN) and the H Fields of Forel.

According to both the International Deep Brain Stimulation Database and Registry and the two meta-analyses [35, 36], no significant differences between targets could be detected. However, both analyses reported that stimulation at the anteromedial GPi resulted in slightly, but non-significantly higher improvement rates compared to thalamic

(centromedian region) DBS—followed by the postero-ventrolateral GPi.

Until today, only three small controlled trials (including 1, 3 and 10 patients, respectively) directly compared two different targets within patients with TS [25, 27, 28]. Houeto et al. [25] ($n=1$) found that stimulation of either target improved tic severity by 70%, markedly ameliorated coprolalia, and eliminated SIB. Welter et al. [27] ($n=3$) reported that GPi stimulation resulted in better tic control compared to thalamic DBS, while simultaneous stimulation at both targets did not result in further improvement. However, only thalamic DBS had a positive effect on depressive mood, emotional hypersensitivity, anxiety, and impulsiveness. Another group also reported about increasing incidence of side effects and decreasing efficacy at long-term follow-up in seven patients after thalamic DBS [37]. Moreover, beneficial effects on tics and global functioning of stimulation of unilateral pallidal and nigral thalamic territories have been reported in two patients who presented predominantly with one-sided (contralateral) tics [123]. Finally, a recently published RCT [28] compared efficacy and safety of bilateral thalamus (CM-Voi) versus pvl GPi versus sham stimulation in severe medically refractory GTS. After 36 weeks GPi DBS—but not thalamic DBS resulted in a significant tic reduction compared to baseline, but had no effect on premonitory urges and psychiatric comorbidities. Direct comparisons of both targets to sham stimulation resulted in inconsistent or negative findings. At long-term follow-up on average 6 years after surgery, at group level no significant improvements could be detected, although single patients continuously benefitted from thalamic DBS. Just recently, Servello et al. [124] published results of a retrospective study comparing effects of CM-Voi ($n=41$) to antero-medial GPi ($n=14$) stimulation. During an evaluation period of 48 months, both targets were equally effective in reducing tics and beneficial effects persisted over time. With respect to OCD, GPi DBS was superior compared to thalamic stimulation.

Based on available data, it is conceivable that in TS, different targets are comparably effective as is the case in DBS in Parkinson's disease. Whether the GPi and thalamic nuclei form an interconnected common network in terms of a network-modulation involved in symptom improvement of TS is currently under investigation. From preliminary experimental studies a new approach has been suggested by selecting individual targets based on the identification of patterns of connectivity [38, 71, 125].

Adverse events

When evaluating the value of DBS in TS, type and frequency of AEs has to be considered too. According to the International Deep Brain Stimulation Database and Registry [33], more than one third of patients (35.4%) experienced AEs. The most frequently reported AEs were stimulation-related (30.8%) and included dysarthria and paresthesias. Dystonia and dyskinesias were more frequently reported after GPi DBS, while paresthesias and weight gain were more frequently reported after thalamic DBS. The only surgery-related AEs (in 3.8%) were hemorrhage found in 1.3% of cases and infections, which occurred with a rate of 2.5%. Only 1.3% of AEs were device-related. Overall, in TS the average rate of AEs after DBS seems to be similar compared to other patient populations such as dystonia and Parkinson's disease [39, 126, 127].

In contrast to the data from the International Deep Brain Stimulation Database and Registry [33], but in line with other studies [24, 25], Servello et al. [72] reported a higher risk of infections in patients with TS (18%, $p<0.001$) compared to other populations. In a recently published meta-analysis in different populations [127], a mean prevalence rate of surgical site infections of 5.0% was reported. Infection rates above average were found in epilepsy (9.5%), dystonia (6.5%), and TS (5.9%), while rates were lower in OCD (4.5%), Parkinson's disease (3.3%), essential tremor (2.9%), and multiple sclerosis (2.4%). It has been speculated that increased infection rate in TS might be related to complications caused by SIB or alternatively to an underlying immunological dysfunction related to the pathology of TS [36]. However, in a recent study based on the cohort of the Tourette Association of America's International Tourette Syndrome Registry and Database [128], the incidence of lead removal was only 5.6% and hence lower than previously reported rates in TS [72]. Infections accounted for nearly half of DBS explantations in this cohort. Partly contradictory data might be explained by lack of harmonized methodology to assess AEs such as a unified questionnaire. Further details of the AE profile reported in RCTs and meta-analyses are given in Table 4.

Recommendations from recently published guidelines

Since the publication of the first ESSTS DBS guidelines in 2011, further guidelines/recommendations specifically for DBS in patients with TS have been published: (i) in 2015 by the Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group [129], (ii) in 2019 by an international team of the American Academy of Neurology (AAN) [5], and (iii) in 2021 by an international group of experts [130]. In addition, in 2014 members of different psychiatric and neurosurgical societies published more general consensus guidelines on DBS in psychiatric disorders [131]. Conclusions from the systematic review of the AAN [5] were that (i) the optimal brain target for DBS in TS is still unknown, (ii) DBS of the anteromedial GPi seems to

Table 4 Adverse effects of DBS in TS

Study	Type of the study	Number of patients included	Total number of different AEs	Stimulation-related AEs*	Procedure-related AEs*	Absolute number of infections
Baldermann et al. [36]	M	156	Not reported	Number of events not reported, descriptive results: gaze disturbances, mood deterioration, dysarthria, psychotic symptoms, erectile dysfunction, memory impairment, anxiety, weight gain, agitation, tiredness, nausea, hypotonia, impulsivity, dizziness, poor balance, speech problems, worsening of tics, hypomania, suicide attempt, apathy	Not reported	Not reported
Coulombe et al. [35]	M	58	16	*N* = 16, tension headache, worsening of preexisting tremor, transient blurring of vision, dizziness, decreased memory, seizure-like episode, suicidal thoughts, decline of attention and mental flexibility, neck tightness, paraesthesias, headedness, parkinsonism, increased OCD, anxiety, agitation, disturbance of eye mobility, dysarthria, nausea, lead removal	*N* = 8, infection, hematoma, wound revision, subcutaneous hydrops, hardware malfunction, lead tip cyst, lead fracture	*N* = 3
Houeto et al. [25]	RCT	1/1*	5	*N* = 5, paraesthesias in the contralateral half of the tongue, contraction of the contralateral half of the body, nausea, hypotonia, and anxiety	*N* = 0	*N* = 0
Maciunas et al. [26]	RCT	5/5*	4	*N* = 2, acute psychosis, recurrence of tics	*N* = 0	*N* = 0
Welter et al. [27]	RCT	3/3*	6	*N* = 6, lethargy, transientcheiro-oral or arm paresthesias, nausea, vertigo, anxiety, libido decrease	*N* = 0	*N* = 0
Ackermans et al. [31]	RCT	6/6*	9	*N* = 5, lack of energy, nystagmus, blurred vision, fixation problem, impaired vertical gaze	*N* = 3, parenchymal hemorrhage, infection, varying motor and psychiatric symptoms (lethargy, binge eating, dysarthria, apathy, gait disturbances and frequent falls)	N = 1
Kefalopoulou et al. [30]	RCT	13/15*	23	*N* = 19, deterioration of condition, hypomania, increased anxiety, insomnia, irritability, tiredness, headaches, mood deterioration, emotional lability, upper-respiratory tract infection, abdominal rush, panic attacks, mild dysarthria, lower limb dyskinesia	*N* = 7, battery infection, prolonged pain around IPG, keloid scar, burr-hole cap discomfort, connection cable discomfort, upper-respiratory tract infection	*N* = 2
Welter et al. [29]	RCT	16/16*	29	*N* = 15, increase in tic severity and anxiety, depression, transient loss of balance, nausea and vertigo, sleep disorder, falls, dysarthria, abnormal movements resembling dyskinesia, weight gain	*N* = 14, infection leading to removal of stimulator and electrodes, misplacement of electrode, serious suffusion around head scar, device migration, headache, asthenia, hardware-related pain,	*N* = 6
Müller-Vahl et al. [28]	RCT	10/10*	20/16	*N* = 31, headache, dizziness, paraesthesia, teeth gnashing, tremor of extremities, tiredness, double vision, dystonic movements of the hand, speech blockade, increase of tics, dysphoria, sleeping problems, deterioration of OCD	N = 5, cable dysfunction, superficial wound infection, chronic infections of stimulator's area (subclavical region)	N = 4
Baldermann et al. [32]	RCT	8/8	12	*N* = 6, Increase in self-injurious behaviors, increased irritability, dysarthria, micrographia	*N* = 2, postoperatively measured increased impedances, discomfort with cable	*N* = 0

DBS deep brain stimulation, *TS* Tourette syndrome, *M* meta-analysis, *RCT* randomized controlled study, *AEs* adverse event(s)

*Given is the total number and in addition a description of each AE

Table 5 Issues on DBS in TS worth of discussion

Clinical problem	Suggestions	Rationale
Age limit	No age limit is recommended	In 2006, an expert group [132] recommended an age limit of 25 years (with rare potential exceptions). However, during the last decades, 58 patients younger than 25 years have received DBS [35]. Since then, different age limits (18 or 21 years) have been suggested by different groups [133]. In 2015, in their updated recommendations Schrock et al. [129] suggested that there should be no age limit, but the decision should be taken individually. Although in the majority of patients tics improve during the course of the disease, it is unclear, whether, when and to what extent severely affected patients may await a significant improvement. Since, there is no evidence that DBS is less efficacious in children, adolescents and young adults with TS—although direct comparisons are missing—evidence is missing justifying any age limit
Functional "tic-like" movement disorder	The diagnosis of a functional "tic-like" movement disorder must be excluded. In particular, co-occurrence of tics and functional "tic-like" movements should be taken into consideration before making the diagnosis of "otherwise treatment-refractory" TS	The diagnosis of a functional movement disorder with "tic-like movements" must be excluded. From clinical experience it can be assumed that the prevalence of functional tic-like movements is increasing and/or physicians are increasingly aware of this phenomenon. Most of these patients present with severe and complex symptoms that do not respond to anti-tic treatments (including antipsychotics and behavioral therapy), and, therefore, might be erroneously misdiagnosed with severe and "treatment-refractory" TS. In addition, there is increasing evidence that in some patients with confirmed TS, in addition, functional tic-like movements coexist. In the literature, this phenomenon has also been described as "tic attacks" [134], since functional tic-like movements may resemble TS-related tic exacerbations. Accordingly, it has been speculated that inconsistent data on DBS in TS might at least in part be influenced by results obtained from patients who suffer—in addition or solely—from functional 'tic-like' movements [135, 136]
Primary treatment goal	The reduction of tics—and not the improvement of comorbidities—should be the primary goal of DBS	Only limited data is available regarding efficacy of DBS on psychiatric comorbidities in TS. While there seems to be some beneficial effect on comorbid depression, effects on OCS and OCD varied, and there seems to be no effect on anxiety and ADHD. Therefore, best possible treatment of psychiatric comorbidities should be established prior to surgery

Table 5 (continued)

Clinical problem	Suggestions	Rationale
Treatment refractoriness	Most authors suggest to assume ''treatment refractoriness'', if behavioral interventions as well as pharmacotherapy with 3 different drugs including both a typical and an atypical antipsychotic in adequate dosage over an adequate period of time do not result in a significant tic reduction or lead to unbearable AEs	There is no generally accepted definition available for ''treatment refractoriness'' in TS. Although different patients may respond in a different way to different antipsychotics, three different drugs seem to be adequate to determine treatment refractoriness. Since clonidine is less commonly used in Europe compared to the USA and many European experts are convinced that clonidine is only effective in case of comorbid ADHD and in these cases less effective compared to antipsychotics, we believe that treatment with clonidine must not be undertaken to determine ''treatment refractoriness''. Although several other drugs have been recommended for the treatment of tics, in Europe none of these drugs is approved or can be recommended without reservation. Although haloperidol is the only drug that is formally licensed in many European countries for the indication tics and TS, due to relevant AEs it can no longer be recommended without restrictions. Since treatment strategies also depend on availability and approval in respective countries, we recommend not to stick to a specific number of different treatments before DBS, but suggest to use at least three different drugs before considering DBS
Target	Altogether eight different targets have been suggested for DBS in TS. Based on current knowledge most experts recommend to use either thalamus (CM–Pf and/or CM–Pf/Voi) or GPi (postero-ventrolateral or anteromedial)	Currently, there are no generally accepted predictors known suggesting superiority of one target over another one. Recommendation for use of thalamus and GPi DBS is largely based on the fact that these targets have been used much more common compared to all other targets. It has been speculated that different targets might be comparable effective, since they may form a common network involved in TS
Number of electrodes and targets	In the vast majority of patients, bilateral stimulation at one target has been performed. Only in single cases unilateral DBS at one target or simultaneous stimulation at two targets has been performed.	Bilateral stimulation at one target is the standard procedure in TS. However, simultaneous implantation of 4 electrodes at two targets has alternatively been suggested to increase options for stimulation without further surgery. If tics mainly occur on one body part, (contralateral) unilateral DBS can be taken into consideration

DBS deep brain stimulation, *TS* Tourette syndrome, *YGTSS* Yale Global Tic Severity Scale, *AEs* adverse events, *GPi* globus pallidus internus, *CM-Pf* centromedian parafascicular, *OCD* obsessive–compulsive disorder, *OCS* obsessive–compulsive symptoms, *ADHD* attention deficit hyperactivity disorder, *AEs* adverse events

be more effective in reducing tics than sham stimulation, (iii) there is insufficient evidence to confirm efficacy of DBS of thalamic nuclei, and (iv) AEs including infection and removal of hardware, appear more common in patients with TS compared to patients receiving DBS for other indications. However, AAN recommendations [5]—as well as the consensus guidelines published in 2014 [131]—deserve some comment regarding the target selection. In both guidelines, an RCT published by Ackermans et al. [31] describing the results of thalamic DBS in TS was not considered, presumably because of the small sample size of only six patients.

The International Deep Brain Stimulation Database and Registry Study Group [129] gave the following recommendations: (i) patients qualified for the procedure should have a diagnosis of TS with severe motor and vocal tics, which did not respond to behavioral interventions per current expert standards and pharmacological treatments from three pharmacological classes (including alpha-adrenergic agonist, two dopamine antagonists (typical and atypical), and a drug from at least one additional class (e.g., clonazepam, topiramate, tetrabenazine)), (ii) DBS should be offered only to patients in centers that have experience with DBS for this indication and after critical evaluation by a multidisciplinary team, (iii) tics as well as psychiatric comorbidities should be assessed and quantified rigorously pre- and post-operatively, and (iv) functional tics and malingering should be considered in the differential diagnosis.

In 2021, Martino et al. [130] suggested the following principles of DBS in TS: (i) tics should be defined as harmful or malignant for a minimum period of 6 months or should be scored as ≥ 35 on the YGTSS-TTS for a minimal period of 12 months, (ii) the patient should report at least moderate impairment on the YGTSS impairment score or high impairment on the Gilles de la Tourette Quality of Life Scale (GTS-QoL) for a minimal period of 12 months, (iii) patients should be treatment resistant defined as no response to behavioral and/or pharmacological interventions, (iv) co-existing psychiatric conditions should be stable for a minimal period of 6 months prior to surgery and primary impairment of quality of life should be caused by tics, and (v) patients should be older than 18, but in severe cases, patients younger than 18 can be considered.

Since the introduction of DBS in TS, recommendations regarding a minimum age for DBS surgery changed substantially. In 2006, the first guidelines of the Tourette Association of America (TAA) proposed a minimum age of 25 years to ensure that individuals would be past the age of potential spontaneous tic improvement as part of the natural course of the disease, before they were implanted with a surgical device [137]. However, more recent guidelines do not recommend such a rigid age limit any more [5, 129, 130]. Compelling arguments have been made for surgical intervention at younger ages in certain cases of severe TS, given the impact extreme tics can have on the emotional developmental, education, professional development, and relationships. However, some expert groups recommend to involve the local ethics committee in patients under the age of 18 before surgery. Similar suggestions have been made in patients where DBS is considered as "urgent" [129, 130, 138].

In summary, recommendations given in the previously mentioned guidelines are (unsurprisingly) largely overlapping with respect to (i) the involvement of a multidisciplinary team consisting of a psychiatrist or neurologist, neurosurgeon, and neuropsychologist, (ii) confirmation of the diagnosis with severe and/or self-injurious tics that are medication- and behavioral therapy-refractory, and (iii) adequate assessment and treatment of psychiatric comorbidities.

Results of the ESSTS survey

Our recent online survey among a large number of ESSTS members ($n = 59$) from 17 different European countries addressed specific questions regarding DBS in TS. Although DBS is offered to patients with TS in the particular region (49%) and center (25%), respectively, and DBS is accessible in the context of both clinical practice (in 29% of centers) and of clinical trials (in 15%), surgery is actually performed only rarely. ESSTS experts estimated to consider DBS in only about 2.5% (mean, $\pm 5.2\%$ (SD)) of their patients. On average, only 2.1 (± 5.7) patients per center recommended for DBS underwent surgery in the past 5 years. There is broad consensus among ESSTS experts to consider DBS only in carefully selected, severely affected and otherwise treatment-refractory patients. Only two experts (3%) reported to consider DBS "routinely, if behavioral and medical (at least three different drugs) treatment failed to improve tics or caused significant AEs", while 17% indicated to consider DBS "not at all/never". The majority of ESSTS members (59%) reported to consider DBS also in patients under the age of 18 years. Remarkably, patients' interest in DBS seems to be low: according to experts' judgement even in specialized centers on average less than two patients/year (mean $= 1.8 \pm 2.7$) ask for DBS.

Although results obtained from the ESSTS survey are affected by several limitations (e.g. small number of participants, no data on how many patients are seen/center relative to those numbers of patients, who were proposed for DBS and who finally underwent surgery in this specific center). However, results from the survey are completely in line with clinical experience in large European TS centers demonstrating that (i) only very few patients ask for DBS, (ii) DBS is recommended only to a very small number of patients, and

(iii) not all patients decide for DBS although recommended by an expert.

Future developments

As a new development in conventional DBS, a new approach is suggested for stimulation of patients with various movement disorders including TS using closed-loop adaptive DBS (aDBS) [139]. With this strategy pathological patterns of neuronal activity are identified [140] allowing flexible dynamic adaptation of stimulation parameters fine-tuned to the concurrent therapeutic demand. This approach might help to decrease the incidence of stimulation-related AEs and to preserve the battery for a longer period of time [97, 141]. A requirement for the development of closed loop DBS for TS is the identification of neurophysiological or clinical markers of tic activity. Recently tic-dependent transient rate changes were found in the activity of individual neurons of the anterior (associative/limbic) GPe and GPi of 8 awake patients during DBS electrode implantation surgeries [98]. Finally, use of tractography may be helpful to optimize the technique, to individualize the targeting, and to increase DBS efficacy [99]. Future developments should focus on the application of these novel techniques to identify non-responders as up to this day it is not clear which parameters predict response to DBS.

Updated recommendations of the ESSTS DBS guidelines group

Currently no definite conclusions can be drawn on efficacy and safety of DBS in TS and many issues are still a matter of debate (Table 5). Therefore, surgical treatment should still be considered as an experimental therapeutic option for carefully selected patients with otherwise treatment-refractory tics. Noteworthy, RCTs consistently reported fewer positive effects on both tics and psychiatric comorbidities compared to data obtained from uncontrolled studies. This fact should also be taken into consideration when interpreting the results from the available data, meta-analyses, and from the International Deep Brain Stimulation Database and Registry, since the majority of these results are based on open and uncontrolled studies. Furthermore, there are specific DBS-related methodological difficulties that may hamper RCTs (e.g., very limited study population meeting inclusion criteria, fixed stimulation parameters vs. individually adapted stimulation parameters, inability of adequate blinding, and handling very severely affected subjects who may suffer from SIB in a clinical trial). Finally, DBS RCTs in psychiatric disorders more often fail to show positive results, or show minor results because of the limited time frame, as in the case of (ALIC) DBS RCTs for OCD [142], and depression [143, 144].

The ESSTS DBS guidelines group has the following recommendations for DBS in TS:

(1) A primary diagnosis of TS according to DSM-5 or ICD-10 criteria must be confirmed. These guidelines do not apply to treatment of patients with secondary tics due to other neurological diseases.
(2) The diagnosis of a functional "tic-like" movement disorder must be excluded. In particular, co-occurrence of tics and functional "tic-like" movements should be taken into consideration before making the diagnosis of otherwise treatment-refractory TS [135].
(3) The reduction of tics—and not the improvement of comorbidities—should be the primary goal of DBS in patients with TS [145]. Adequate treatment of psychiatric comorbidities should be established prior to surgery.
(4) DBS should be taken into consideration only in patients with tics that cause significant impairment in patients' quality of life and that are resistant to established conservative treatment strategies including behavioral and pharmacotherapy. Because (i) treatment strategies for tics differ from country to country, (ii) treatment strategies are based on availability of therapies, and (iii) an established definition for "treatment refractoriness" is still lacking, the working group decided not to recommend a specific treatment algorithm before considering DBS. However, before undergoing DBS the patient should be regarded as "otherwise treatment-refractory" in the opinion of a multidisciplinary team which includes refractoriness to both behavioral and pharmacotherapeutical interventions [131].
(5) Both expected treatment efficacy and tolerability must be taken into consideration before the decision on DBS is taken.
(6) We do not recommend a minimum age for operation. However, physicians should be aware that (i) tics often improve spontaneously after puberty and in early adulthood, (ii) the typically spontaneous improvement of tics with increasing age should be thoroughly discussed, (iii) in children—as in adults—abrupt and tremendous deterioration of symptoms might be related to the onset of comorbid functional "tic-like" movements [134] and not as a result of an increase of tics caused by TS, (iv) there is only very limited information on the efficacy of DBS in children with TS, and (v) in children and adolescents involvement of the local ethics committee is recommended.
(7) DBS should be performed in specialized centers by a dedicated multidisciplinary team including a psychi-

atrist, psychologist and/or neurologist trained in the treatment of patients with TS. This multidisciplinary approach is not only required preoperatively (e.g. for correct diagnosing and assessment of inclusion criteria and judgement on "treatment-refractoriness"), but also during follow-up treatment with regular consultations of both surgical as well as psychiatric or neurological experts.

(8) If possible, DBS should be performed following a specified protocol and within the context of a controlled trial, a cohort study, or registry database, but at least should include systematic pre- and post-DBS assessment of tics, premonitory urges, psychiatric comorbidities (including at least ADHD, OCD, depression, and anxiety), and quality of life.

(9) Physicians should be aware and take into consideration that AEs—and in particular infections—might be more common in patients with TS.

(10) Since it is still unclear, which target is most effective in TS in general and specifically for tic reduction, we do not recommend using a particular target. Based on current data different parts of the thalamus (CM–Pf and CM/Voi) as well as the postero-ventrolateral and the anteromedial part of the GPi seem to generate comparable results. Long-term follow-up of patient characteristics is essential and systematic documentation of long-term outcomes may help disentangle whether specific features of TS are more likely to be responsive to thalamic or pallidal DBS.

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