Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: [redacted]	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]	

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Tourette's Disorder 307.23

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

see attached

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

see attached N/A

Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

see attached [redacted] was recently diagnosed with, C5-7 radiculopathy causing pain in her hands

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

see attached

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

see attached

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

see attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Signature: ▶ [redacted]	Date Signed: 2 April 2014

Section C.1

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

Diagnosing Tic Disorders

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*)[1 (#ref)] is used by health professionals to help diagnose tic disorders.

Tics are sudden twitches, movements, or sounds that people do repeatedly. People who have tics cannot stop their body from doing these things. For example, a person with a motor tic might keep blinking over and over again. Or, a person with a vocal tic might make a grunting sound unwillingly.

Three tic disorders are included in the *DSM-5*:

- Tourette's disorder (also called Tourette Syndrome [TS]) (#TS)
- Persistent (also called chronic) motor or vocal tic disorder (#persistent)
- Provisional tic disorder (#provisional)

The tic disorders differ from each other in terms of the type of tic present (motor or vocal, or a combination of both), and how long the symptoms have lasted. People with TS have both motor *and* vocal tics, and have had tic symptoms for at least 1 year. People with persistent motor or vocal tic disorders have either motor *or* vocal tics, and have had tic symptoms for at least 1 year. People with provisional tic disorders can have motor or vocal tics, or both, but have had their symptoms less than 1 year. The criteria for diagnosis have been updated with the recent publication of the 5th edition of the DSM. One change was to use the term 'provisional' tic disorder rather than 'transient' tic disorder for tics that started less than a year before diagnosis. In DSM-IV, a diagnosis of TS or persistent tic disorder required that there was no tic-free period of 3 months or more in the year prior to diagnosis. This is no longer required.

Here are the criteria in shortened form. Please note that they are presented for your information only and should not be used for self-diagnosis. If you are concerned about any of the symptoms listed, you should consult a trained health care provider with experience in diagnosing and treating tic disorders.

The criteria are presented here in modified form to make them more accessible to the general public. They are listed here for information purposes only and should not be used for self-diagnosis. If you are concerned about any of the symptoms listed, you should consult a trained health care provider with experience in diagnosing and treating tic disorders.

Tourette Syndrome (TS)

For a person to be diagnosed with TS, he or she must:

- have both multiple motor tics (for example, blinking or shrugging the shoulders) *and* vocal tics (for example, humming, clearing the throat, or yelling out a word or phrase), although they might not always happen at the same time.
- have had tics for at least a year. The tics can occur many times a day (usually in bouts) nearly every day, or off and on.

- have tics that begin before he or she is 18 years of age.
- have symptoms that are not due to taking medicine or other drugs or due to having another medical condition (for example, seizures, Huntington disease, or postviral encephalitis).

Persistent (Chronic) Motor or Vocal Tic Disorder

For a person to be diagnosed with a persistent tic disorder, he or she must:

- have one or more motor tics (for example, blinking or shrugging the shoulders) or vocal tics (for example, humming, clearing the throat, or yelling out a word or phrase), but *not* both.
- have tics that occur many times a day nearly every day or on and off throughout a period of more than a year.
- have tics that start before he or she is 18 years of age.
- have symptoms that are not due to taking medicine or other drugs, or due to having a medical condition that can cause tics (for example, seizures, Huntington disease, or postviral encephalitis).
- not have been diagnosed with TS.

Provisional Tic Disorder

For a person to be diagnosed with this disorder, he or she must:

- have one or more motor tics (for example, blinking or shrugging the shoulders) or vocal tics (for example, humming, clearing the throat, or yelling out a word or phrase).
- have been present for no longer than 12 months in a row.
- have tics that start before he or she is 18 years of age.
- have symptoms that are not due to taking medicine or other drugs, or due to having a medical condition that can cause tics (for example, Huntington disease or postviral encephalitis).
- not have been diagnosed with TS or persistent motor or vocal tic disorder.

Related Pages

- Other Concerns and Conditions (/ncbddd/tourette/otherconcerns.html)
- Attention-Deficit/Hyperactivity Disorder (ADHD) (/ncbddd/adhd)
- Child Development (/ncbddd/child/default.htm)
- Positive Parenting Tips (/ncbddd/child/positive.htm)
- CDC's National Center on Birth Defects and Developmental Disabilities (/ncbddd/index.html)

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

Page last reviewed: February 20, 2014
Page last updated: February 20, 2014
Content source: National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

Centers for Disease Control and Prevention 1600 Clifton Rd. Atlanta, GA 30333, USA
800-CDC-INFO (800-232-4636) TTY: (888) 232-6348 - Contact CDC-INFO

Section C.2

DEPRESSION AND ANXIETY 27:600–610 (2010)

Review

TIC DISORDERS: SOME KEY ISSUES FOR DSM-V

John T. Walkup, M.D.,[1*] Ygor Ferrão, M.D. M.Sc.,[2] James F. Leckman, M.D.,[3] Dan J. Stein, M.B.,[4] and Harvey Singer, M.D.[5]

This study provides a focused review of issues that are relevant to the nosology of the tic disorders and presents preliminary recommendations to be considered for DSM-V. The recommended changes are designed to clarify and simplify the diagnostic criteria, reduce the use of the residual category, tic disorder not otherwise specified, and are not intended to alter substantially clinical practice or the continuity of past and future research. Specific recommendations include: (1) a more precise definition of motor and vocal tics; (2) simplification of the duration criterion for the tic disorders; (3) revising the term "transient tic disorder" for those with tic symptoms of less than 12-month duration; (4) establishing new tic disorder categories for those with substance induced tic disorder and tic disorder due to a general medical condition; and (5) including a motor tic only and vocal tic only specifier for the chronic motor or vocal tic disorder category. Depression and Anxiety 27:600–610, 2010. © 2010 Wiley-Liss, Inc.

The tic disorders are childhood onset neuropsychiatric disorders commonly associated with other psychiatric disorders including attention deficit hyperactivity disorder and obsessive–compulsive disorder.[1] Although the cause of the tic disorders is not known there have been substantial advances in our understanding of the phenomenology,[2] epidemiology,[3] genetics,[4] pathophysiology,[5,6] course,[7] and treatment[8,9] of these disorders since the last version of DSM was published.

The tic disorders were first included in DSM-III[10] and there have been three important changes to the criteria in subsequent editions. In DSM-IV[11] the age of onset was changed from before 21 years to before 18 years and an impairment criterion was added and required for diagnosis. In DSM-IV-TR[12] the impairment criterion was removed, due to concerns regarding patients who had the cardinal features of Tourette's disorder (i.e. chronic motor and vocal tics), but who did not experience impairment.[13,14]

This review focuses on nosological issues specific to revision of the tic disorder diagnostic categories and criteria for DSM-V in light of the clinical and research knowledge that has accumulated since the publication of DSM-IV. Although our understanding of the epidemiology, genetics, course, and treatment of the tic disorders has improved substantially since DSM-IV, the core phenomenology of the tic disorders as described over a century ago by Gilles de la Tourette is essentially unchanged.[15] Recommendations for changes to the diagnostic criteria are intended to clarify and simplify the diagnostic criteria and are not intended to alter substantially clinical practice or the continuity of past and current research.

[1]Department of Psychiatry, Division of Child and Adolescent Psychiatry, Weill Cornell Medical College, New York, New York
[2]Department of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil
[3]Yale Child Study Center, New Haven, Connecticut
[4]Department of Psychiatry, University of Cape Town, Cape Town, South Africa
[5]Department of Neurology, Division of Child Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland

*Correspondence to: John T. Walkup, Division of Child and Adolescent Psychiatry, Weill Cornell Medical College, Box 140, 525 E. 68th Street, New York, NY 10065.
E-mail: j.walkup@med.cornell.edu

This Article is being co-published by *Depression and Anxiety* and the American Psychiatric Association.

Conflict of Interest Statement: John Walkup is Chair of the Medical Advisory Board of the Tourette Syndrome Association, receives honoraria for talks presented on behalf of the joint CDC-Tourette Syndrome Association educational outreach program. He also receives royalties from Guildford and Oxford Press for books on Tourette syndrome.

Received for publication 30 December 2009; Revised 11 April 2010; Accepted 15 April 2010

DOI 10.1002/da.20711
Published online in Wiley InterScience (www.interscience.wiley.com).

This study was commissioned by the DSM-V Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group. It represents the work of the authors for consideration by the work group. *Recommendations provided in this study should be considered preliminary at this time; they do not necessarily reflect the final recommendations or decisions that will be made for DSM-V, as the DSM-V development process is still ongoing.* It is possible that this study's recommendations will be revised as additional data and input from experts and the field are obtained.

CURRENT TIC DISORDER DIAGNOSTIC CRITERIA

There are four tic disorder diagnostic categories included in the DSM-IV-TR section of Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence:[12] (1) Tourette's disorder (TD); (2) chronic motor or vocal tic disorder (CMVTD); (3) transient tic disorder (TTD); and (4) tic disorder, not otherwise specified (TDNOS) (Table 1). Diagnostic decisions for the tic disorders in DSM-IV-TR are based on the presence of motor and/or vocal tics, duration of tic symptoms, age of onset, and absence of any known cause such as a general medical condition or substance use. Other diagnostic schemas, such as ICD-10[16] and those developed for genetic and epidemiological studies,[17] will not be reviewed in detail here.

ISSUES TO BE ADDRESSED

1. Are any changes required to the definition of tics in criterion A of the current diagnostic criteria?

- Should vocalizations that are caused by muscle contractions be considered vocal tics or motor tics?
- Would it aid in the distinction of tics from stereotypies to remove the term "stereotyped" from the description of tics in Criterion A?
- Are wording changes needed to make Criterion A consistent in each of the tic disorder diagnoses?
- As both TD and CMVTD are chronic tic disorders should Criterion A for TD and CMVTD be changed to allow merging of these categories?
- Is there sufficient distinction between chronic motor tic disorder and chronic vocal tic disorder to justify making each a unique diagnostic category?

2. Are any changes required to Criterion B for any of the tic disorder diagnoses?

- There are three issues relevant to the duration criterion for TD, CMVTD and TTD.
  - Is the 12-month duration of symptoms appropriate for diagnosis?
  - Is the maximum 3-month tic-free interval in any 12-month interval critical to the determination of chronicity?
  - Is a change needed for the duration criterion (Criterion B) in TTD?

3. Are any changes required to Criterion C for any of the tic disorder diagnoses?

- Is the 18-year maximum age of onset too old?

TABLE 1. DSM-IV TR for the tic disorders

DSM-IV-TR Criteria 307.23 (Tourette's Disorder)

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization)
B. The tics occur many times a day, (usually in bouts,) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months
C. The onset is before age 18 years
D. The disturbance is not due to the direct physiological effects of a substance (e.g. stimulants) or a general medical condition (e.g. Huntington's disease or postviral encephalitis)

DSM-IV-TR Criteria 307.22 (Chronic Motor or Vocal Tic Disorder)

A. Single or multiple motor or vocal tics (i.e. sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations), but not both, have been present at some time during the illness
B. The tics occur many times a day nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months
C. The onset is before age 18 years
D. The disturbance is not due to the direct physiological effects of a substance (e.g. stimulants) or a general medical condition (e.g. Huntington's disease or postviral encephalitis)
E. Criteria have never been met for Tourette's disorder

DSM-IV-TR Criteria 307.21 (Transient Tic Disorder)

A. Single or multiple motor and/or vocal tics (i.e. sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations)
B. The tics occur many times a day, nearly every day for at least 4 weeks, but for no longer than 12 consecutive months
C. The onset is before age 18 years
D. The disturbance is not due to the direct physiological effects of a substance (e.g. stimulants) or a general medical condition (e.g. Huntington's disease or postviral encephalitis)
E. Criteria have never been met for Tourette's disorder or chronic motor or vocal tic disorder

Specify if:
Single Episode or Recurrent

DSM-IV TR Criteria 307.20 (Tic Disorder, Not Otherwise Specified)
This category is for disorders characterized by tics that do not meet criteria for a specific tic disorder. Examples include tics lasting less than 4 weeks or tics with an onset after age 18 years

4. Are any changes required to Criterion D for any of the tic disorder diagnoses?

- Should prescription stimulant medication be used as an example of substances causing tics?
- Should the current exclusion criteria be retained?

5. Is any change required for Criterion E for CMVTD and TTD?

6. Is there a need for a clinical severity criterion or specifier?

- Should there be a clinical severity criterion or specifier for the tic disorders?

7. Does the Tic Disorder, Not Otherwise Specified category need revision?

- Should those with very short duration of tic symptoms be included in the proposed category of provisional tic disorder?
- Should adult onset cases continue to be included in TDNOS category?

8. Do tic disorder diagnostic criteria appear suitable from a developmental, gender, and cross-cultural perspective?

9. Are there subtypes of tic disorders supported by the literature that should be included in DSM-V?

- Is there substantial enough an evidence base for subtypes of tic disorders?

10. Is the current grouping of the tic disorders in DSM-IV-TR appropriate?

SIGNIFICANCE OF THE ISSUES

With respect to issues #1–7, the aim of the diagnostic criteria for tic disorders is to classify patients' symptoms accurately, so as to improve treatment. The diagnostic criteria also facilitate provider communication about the patient and allow research to be conducted to improve our understanding of the epidemiology, genetics, pathophysiology, course and prognosis, and management of tic disorders. Emphasis will be placed on addressing the shortcomings of the current criteria, and potential ways of addressing these.

With respect to issue #8, there is a great interest in reviewing the current DSM-IV-TR criteria to ensure that they fully account for any developmental variability in symptom presentation, and optimally reflect potential gender, racial or ethnic differences in symptoms, onset, and course.

With respect to issue #9, since DSM-IV-TR there has been a great deal of research on the phenomenology of tic symptoms, including factor analyses that suggest grouping of tic symptoms that may have utility in assessment, identifying patterns of co-morbidity or differences in course of illness, and treatment planning.

Issue #10 addresses with which other disorders should the tic disorders be grouped. This is a particularly challenging issue facing DSM-V. How the tic disorders are grouped communicates how the field perceives the relationships between the tic disorders and psychiatric disorders in general, and has implications for patients, providers, and payers, and for advocacy that needs to be carefully considered. This issue will also be considered in more detail in a separate study in this issue (Phillips et al.).

SEARCH METHODS

A literature search was conducted using WebofScience, PubMed, Psychinfo, and other relevant databases. Documents from the DSM-V planning process (e.g. Research Agenda books, the Options Book, and planning conferences) and Reference sections of published articles were also examined. There was no time limit to the search. Search terms included "tic disorders," "tics," "Tourette disorder," "Tourette's disorder," "Tourette syndrome," "Tourette's syndrome," "Tourettes," "premonitory sensation," and "premonitory urge."

RESULTS

1. Are any changes required to the definition of tics in criterion A of the current diagnostic criteria?

- Should vocalizations that are result of motor tics be considered vocal tics or motor tics?

Motor tics of the diaphragm and oropharynx can result in simple vocalizations (e.g. grunting, snorting, and sniffing).[18] Whether such simple sounds are considered motor or vocal tics have important implications for the tic disorder diagnoses. Retaining the motor and vocal tic distinction, is arguably in keeping with the descriptive approach in DSM-V. Changing diagnostic practice and reclassifying simple vocalizations as motor tics might be more accurate but such a change in diagnostic practice would result in significant discontinuity with historical diagnostic approaches in clinical and research practice. For example, individuals with simple vocalizations who currently carry the diagnosis of TD may no longer meet the diagnostic criteria for TD, and prevalence estimates from recent high-quality epidemiological studies[3] using the current criteria may shift substantially. Furthermore, there is no evidence that such a change would improve the assessment or treatment of patients with tic disorders.

In addition to the historical precedent, and the descriptive nature of DSM, there is empirical data to support the distinction between motor and vocal tics. Specifically, factor analytic studies consistently identify motor and vocal tics as independent factors.[19–22]

Epidemiological studies suggest that co-morbidity rates differ based on the presence chronic motor or chronic vocal tics. The presence of chronic vocal tics is associated with higher rates of co-morbidity than chronic motor tics (58% vs. 12%) as well as specifically higher rates of ADHD (33% vs. 12%) and OCD (8% vs. 0%).[23]

Recommendation: We recommend continuing to identify vocalizations caused by motor tics as vocal tics.

- Would it aid in the distinction of tics from stereotypies to remove the term "stereotyped" from the description of tics in Criterion A?

Tics and stereotypies can be difficult to differentiate from each other. Both can have an onset in early childhood and can co-occur in the same child.[24] In addition, complex tics may appear similar to stereotypies.[24] Including the word "stereotyped" in the definition of a tic may contribute to the misclassification of stereotypies and tics. Given that there are other terms that can capture the repetitive nature of tics, eliminating the word stereotyped from the definition of a tic would remove one source of potential confusion. Although there are few other terms that capture the fact that tics are consistent both within a patient and across patients, removing the term "stereotyped" from the definition of a tic, using simpler and more descriptive language to define tics and providing examples of tics and stereotypies in the text, would address potential confusion and help clinicians in distinguishing these symptoms.

Recommendation: We recommend removing the term "stereotyped" from the definition of a tic in Criterion A, and providing detailed descriptions and examples of tics and stereotypies in the text on tic disorder and stereotypic movement disorder. See Criterion A tic definition below.

- Are wording changes needed to make Criterion A consistent in each of the tic disorders?

The definition of a tic that is used in Criterion A for TD, DMVTD, and TTD varies in its wording. The definition of a tic should be consistent across the tic disorders.

Recommendation: We recommend a consistent definition of tics in Criterion A for TD, CMVTD, and TD namely, "A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization."

- As both TD and CMVTD are chronic tic disorders should Criterion A for TD and CMVTD be changed to allow merging of these categories?

Based on Criterion A, patients with chronic motor and vocal tics are diagnosed with TD, while those with chronic motor only or chronic vocal only are diagnosed with CMVTD. Eliminating the distinction between TD and CMVTD might potentially simplify diagnostic assessment by eliminating a distinction between the chronic tic disorders—TD and CMVTD. Although research is lacking, there are likely few differences in neural substrates, genetic and environmental risk factors, course or treatment response that justify a major distinction between TD and CMVTD.[25] In addition, some genetic[26,27] and treatment studies[28,29] combine TD and CMVTD.

However, there are important disadvantages to eliminating the distinction between TD and CMVTD. There is an emerging literature that suggests that the presence of vocal tics in TD may be clinically meaningful. For example, impairment associated with TD appears to be greater than that for chronic motor tics only.[30] As noted above, factor analytic studies of TD suggest the presence of vocalizations, especially complex vocalizations, to be an important phenotypic distinction to maintain.[19–22,31,32] In addition, co-morbidity patterns may differ between TD and CMVTD.[33] Collapsing these diagnostic categories may therefore lead to important loss of information, and adversely impact assessment and treatment.

Recommendation: We recommend that the distinction between Tourette's disorder and the chronic motor or vocal tic disorder be maintained.

- Is there sufficient distinction between individuals with chronic motor tics only and chronic vocal tics only to justify making each a unique diagnostic category?

Currently, patients with chronic motor tics only or chronic vocal tics only are diagnosed with chronic motor or vocal tic disorder. There may be advantages to create a new diagnostic category for patients with only motor tics or only vocal chronic tics. As noted earlier, vocal tics may reflect a different neurobiology and may potentially require different treatment. However, the prevalence of chronic vocal tic disorder is relatively low,[23] and to date no study has suggested that motor or vocal tics should be treated differently. It is possible that those who report only vocal tics may in fact have motor tics upon examination as in clinical practice and in research it is common to observe tics in those who do not report any tic symptoms.[34]

Recommendation: We recommend maintaining the current category of chronic motor or vocal tic disorder, but adding a motor tic only vs. vocal tic only specifier. This change in diagnostic practice may stimulate research into a small, but potentially meaningful subtype of tic disorder.

2. Are any changes required to Criterion B for any of the tic disorder diagnoses?

- There are three issues relevant to the duration criterion for TD, CMVTD, and TTD.
  - Is the 12-month duration of symptoms adequate for diagnosis?
  - Is the maximum 3-month tic-free interval in any 12-month interval critical to the determination of chronicity?
  - Is a change needed for the duration criterion (Criterion B) in TTD?

The 12-month minimum duration of symptoms is an arbitrary cut-off point. Yet, it is consistent with the term "chronic" and has historical precedent in DSM. Although 12 months of persistent symptoms may be considered a high threshold for chronicity, it assures that the chronic tic disorder diagnoses are only used for those with persistent tic symptoms. This is especially important given that up to a third of those with tics in childhood become tic-free or nearly tic-free in adulthood.[35,36]

Although the minimum duration of tic symptoms that predicts a chronic course is not known,[37] there could be value to a shorter duration criterion. A shorter duration criterion would allow more children to have the diagnosis and potentially increase referral for early interventions for the common and disabling co-occurring conditions. Also, such early diagnosis could increase referrals for promising low-risk behavioral interventions[38,39] for these disorders.

Given the waxing and waning nature of the tic disorders, including a maximum tic-free interval is a way of making sure that those who are diagnosed with a chronic tic disorder have persistent and not transient symptoms. However, the duration of the tic-free interval in DSM is arbitrary,[18] is not based on data, and is potentially more difficult to assess (i.e. based on a patient's recall of tic-free periods) than the 12-month duration criteria. As noted above individuals are often unaware of their current tic symptoms,[34,40] so that some individuals who report tic-free intervals may, when examined, not be tic free.

Given the 12-month minimum duration for TD and CMVTD there is a need for a diagnostic category for those with tic disorders of less than 12-months duration. Currently, the transient tic disorder (TTD) diagnosis is intended for those who have not had tics for the minimum 12 months necessary for a chronic tic disorder diagnosis. However, the current TTD category is awkward in its implementation. First, the term "transient" suggests that the tics have come and gone. For a youngster who presents with 6 months of tic symptoms, it is awkward to describe the child's symptoms as transient when they are currently present and have been persistent for 6 months. Second, that same youngster does not actually qualify for a TTD diagnosis until evaluated again at 12 months where upon the youngster can get either a TTD diagnosis, if the tics went away, or a TD or CMVTD diagnosis, if the tics persist. The TTD, recurrent, category is similarly awkward to implement; for example, an 11-year-old patient with age of tic onset at 7 years who has multiple episodes of motor and vocal tics of less than 12 months duration and with greater than 3 month tic-free intervals will receive a diagnosis of TTD, recurrent. Clinically, this patient has chronic symptoms over a 4-year period. In clinical practice this patient would likely be considered to have chronic symptoms of Tourette's disorder diagnosis, but under the current criteria would only meet criteria for a transient tic disorder, recurrent.

Currently, those with tics of less than 4 weeks duration receive a TDNOS diagnosis. Again, the 4-week threshold is arbitrary, not based in data and it is unknown whether tics of less than one month's duration predicts a transient course or not.

Recommendation: We recommend maintaining the 12-month duration criterion, eliminating the 3-month maximum tic-free interval, and changing the wording of the duration criterion for TD and CMVTD. The new wording would be "The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset." Thus, chronicity would be determined by the duration of symptoms from first tic onset rather, rather than by persistence of symptoms over any arbitrary 12-month period.

We also recommend changing the name of the TTD diagnostic category to "provisional tic disorder" and revising its duration criterion. The use of the diagnosis "provisional tic disorder" seems more accurate than "transient tic disorder" for patients with ongoing tic symptoms of less than one-year duration since onset. The use of a "provisional tic disorder" diagnosis acknowledges that a patient presently has tics, but which have not been persistent for more than 12 months since first onset. To be consistent with the wording of the duration criterion for TD and CMVTD (i.e. Criterion B), the duration criterion for the provisional tic disorder category would be "The tics have been present for less than 1 year since first tic onset."

We recommend that children with symptoms of less than 4 weeks also be given the provisional tic disorder diagnosis. This change would reduce the use of the residual category, TDNOS, for very new onset cases.

3. Are any changes required to Criterion C for any of the tic disorder diagnoses?

- Is the 18-year maximum age of onset too old?

In DSM-IV the maximum age of onset for the tic disorders was changed from 21 to 18 years. This change reflects multiple studies suggesting that the age of onset was in children and young adolescents.[36] Also, age 18 corresponds to an accepted standard of when adulthood begins. This age of onset has been consistently used in DSM despite prior and current research, which suggests the age of onset for most affected individuals to be even earlier, prior to puberty.[36,41] Given the precedent for the upper age limit of 18 years, the cultural acceptance of age 18 as the age of adulthood and the listing of the tic disorders in the section on Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence, having a generous age of onset criterion allows for inclusion of all typical and atypical cases that might have had tic onset in the mid to late teen years.[41]

Recommendation: We recommend maintaining the age 18 years as the upper age limit of tic onset.

4. Are any changes required to Criterion D for any of the tic disorder diagnoses?

- Should prescription stimulant medication be used as an example of substances causing tics?

The current exclusion criterion excludes tics that clearly appear secondary to substance use (e.g. stimulants) or a general medical conditions. Although this exclusion is consistent with an anecdotal literature suggesting stimulant medication can cause new tic onset or an exacerbation of existing tics,[42,43] and current product information for stimulant medications, it is not consistent with the current evidence base of stimulant treatment in children with tics and ADHD. Blinded clinical trials of stimulant medications for ADHD in children with tics suggest that stimulants are no more commonly associated with tics as an adverse event than placebo or clonidine.[28] These data and other studies[44–46] suggest that during well-supervised stimulant treatment of ADHD in children with tics, the rate of tic exacerbation associated with stimulant treatment is not higher than that observed with placebo or an active drug comparator.

Recommendation: We recommend removing the example of prescription stimulants medication from the exclusion criteria to make the diagnostic criteria consistent with the treatment evidence base for the stimulant treatment of ADHD in children with tic disorders. We also recommend using examples of illegal substances such as cocaine to highlight the potential adverse effects of drugs of abuse in people with tics.

- Should the current exclusion criteria be retained?

The current exclusion criterion assures that tic symptoms in those who are diagnosed with TD, CMVTD, or TTD are idiopathic as to cause and are not the result of a known medical cause or substance induced. There is a strong precedent to exclude from a tic disorder diagnosis (and any other psychiatric disorder) those whose symptoms appear to be attributable to an identifiable cause. However, caution is warranted in attributing a specific cause to tic onset or worsening as there is potential for a false attributions. Tics are common in childhood, tics wax and wane in severity and are responsive to environmental factors such as psychological stress or excitement, and thus may appear to come and go in response to environmental factors. For example, it is common in clinical practice for children and parents to attribute tic onset or worsening to a situation, event or environmental factor because of a close temporal association and a plausible mechanism (e.g. stress at school, excitement at an amusement park, etc.) The exclusion is not meant for such cases with a typical age of onset, pattern of symptoms, whose onset or worsening are temporally associated with routine experiences of childhood. Rather the exclusion is meant to highlight those cases where tic onset or exacerbation is associated with unusual events, which directly affect central nervous system functioning, are temporally associated with tic onset and may have other atypical features. For example, most adult onset cases are readily attributable to medical condition, although the phenomenology of such secondary tics is not different than tics that are considered idiopathic and treatment of such secondary tics is similar to that for idiopathic tics.[47]

Recommendation: We recommend retaining the current exclusion criterion for the tic disorders, but also recommend creating new categories in parallel with other DSM diagnoses for those tic disorders where there is a known cause. Tic disorders due to a misuse of an illegal substance (such as cocaine[48]) should be classified as Substance (indicate the substance) Induced Tic Disorder and those tic disorders with a known medical cause (such as stroke, encephalitis, or head trauma[48]) should be diagnosed with "Tic Disorder due to ..." (indicate the general medical condition).

5. Is any change required for Criterion E for CMVTD and TTD? Criterion E notes the hierarchical nature of the tic disorders such that those with a Tourette disorder history cannot be given subsequently a chronic motor or vocal tic disorder. We do not recommend a change to this criterion.

6. Is there a need for a clinical severity specifier?

- Should there be a clinical severity criterion or specifier for the tic disorders?

In DSM-IV, all the tic disorder diagnoses included a distress or impairment criterion that was required for diagnosis. This criterion was removed from the tic disorders in DSM-IV-TR as many individuals with chronic motor and/or vocal tics were not considered distressed or impaired and therefore could not be diagnosed with a tic disorder.[13,14]

There are a number of factors that contribute to tic severity or impairment in patients with tic disorders.[49,50] The person's reaction to his or her tics, the family's reaction, and the reaction of others at school or work place may all impact perceived severity or impairment and render such assessments highly variable and potentially unreliable. For example, clinical experience suggests that a child with mild tics in a hostile school environment may be more impaired, and perceived as having more severe symptoms than a child with more severe tics in an accepting school environment. Also, as many who come to clinical attention have tics and co-morbid conditions, parsing tic impairment and severity from severity and impairment associated with co-occurring conditions is difficult.

Recommendation: We do not recommend that severity or impairment be included as a criterion required for diagnosis. However, consideration should be given to develop criteria to specify a level of severity or impairment for those diagnosed with a tic disorder.

7. Does the Tic Disorder, Not Otherwise Specified category need revision? Currently, the TDNOS category is to be used (1) for those with very short duration of symptoms (i.e. less than 4 weeks); and (2) onsets of symptoms that occur after age 18 years.

- Should those with very short duration of tic symptoms be included in the new provisional tic disorder category?

There are no data to suggest that those with tics of less than 4 weeks duration are substantially different from those with tics greater than 4 weeks duration or that the phenomenology of the tics are different than those with tics of greater duration.

Recommendation: We recommend that those with any duration of tic symptoms of less than 12 months since tic onset be diagnosed with a provisional tic disorder. This will reduce the use of TD NOS for such new onset cases.

- Should adult onset cases continue to be included in TDNOS category?

Although the typical age of onset of the tic disorders is in the early childhood years, a number of case reports have documented the onset of tics in the adult years.[47] First clinical presentations of tics in adulthood include those who have known of their lifetime history of tics, those who through careful evaluation are found to have a childhood onset, and those who appear to have an onset in adulthood.[47] Of the cases with verified adult onset, most had an identifiable medical cause and very few were considered idiopathic. These idiopathic adult onset cases do not appear to differ from age-matched affected adults with childhood onset.[47]

Recommendation: For those adult onset cases with an identifiable medical cause we recommend using the new category "Tic Disorder due to... indicate the medical condition" that would include motor and/or vocal tics of any age of onset (See proposed criteria). Idiopathic adult onset cases would continue to be diagnosed with TDNOS. This will eliminate the use of TDNOS for adult onset cases with an identifiable medical cause.

8. Do tic disorder diagnostic criteria appear suitable from a developmental, gender, and cross cultural perspective?

Although tics wax and wane in severity and tic symptoms can be highly variable within and across individuals, there are no data suggesting that the phenomenology or treatment of tics are different for children, adolescents, or adults,[9] for males and females or across cultures.[51] However, some studies have found that girls may have different patterns of onset and course,[52] co-morbidity,[41] or neuroimaging findings.[53]

Recommendation: We do not recommend any change in diagnostic criteria to specifically reflect developmental, gender, or cross-cultural issues.

9. Are there subtypes of Tic Disorders supported by the literature that should be included in DSM-V?

- Is there substantial enough an evidence base for subtypes of tic disorders?

A number of factor analytic studies have suggested that there are distinct symptom groupings which might have important implications for understanding the genetics and pathophysiology of the tic disorders and may also have implications for treatment.[19–22] The results of these studies suggest that impairment associated with combined motor and vocal tics appears to be greater than with chronic motor tics alone, and supports the distinction of TD from CMVTD. Some studies have identified factors for simple tics and complex motor and vocal tics.[21] Others have found complex motor, complex vocal tics, and simple motor and vocal tics to be important constructs.[19] These studies combined suggest that simple and complex tics, and vocal tics appear to be unique constructs. Methodological differences and shortcomings including small sample sizes and varying sampling strategies (e.g. large kindreds, population isolates, and clinic populations) lessen enthusiasm for supporting diagnostic changes based on these studies. Also, a number of the factor analytic studies have included not just tic symptoms but symptoms of co-morbid conditions so that the factors are an amalgam of tic disorder and symptoms from other co-occurring disorders.

Ultimately subtyping the tic disorders would allow for the identification and assessment of distinct phenotypes for research studies, but even if validated such subtypes may not be useful for clinical purposes.

Recommendation: Given the lack of empirical support for specific subtypes and limitations of the factor analytic studies, we do not recommend creating subtypes of TS at this time. We believe this will not impact adversely on future research, given that the Methods section of these manuscripts provide adequate detail for replication. We also recommend that the accompanying text include a discussion of factor analytic studies and potential for subtyping in the future.

10. Is the current classification of the tic disorders appropriate?

In DSM-IV-TR the tic disorders are grouped with "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence."[12] At the DSM-V Research Planning Conference on Obsessive–Compulsive

Spectrum Disorders in 2006,[54] consideration was given to an OC Spectrum Disorders grouping (Please see Phillips et al., this issue for a complete discussion of this issue).

There are a number of reasons for and against grouping the tic disorders with other disorders, such as OCD, that are characterized by repetitive thoughts and behaviors. Tic disorders, OCD, and other candidate conditions for the OC Spectrum disorders are characterized by repetitive behaviors that are consistent within a patient and can be manifested similarly among patients.[55] Although tics are readily distinguished from other repetitive behaviors, some complex tics can appear goal-directed and similar to compulsions. The tic disorders and obsessive–compulsive disorder are also similar in that patients describe internal experiences (i.e. obsessions in OCD and premonitory urges in the tic disorders) that can occur before or prompt a tic or compulsion.[56] However, the internal experiences in OCD and the tic disorders are different as obsessions in OCD are often complex cognitions that included autonomic arousal, whereas patients with Tourette's disorder report more sensory experiences or urges and less cognitive symptoms.[57–59] The tic disorders and OCD are commonly co-morbid with each other suggesting an etiological link,[2] but some symptoms of OCD are more commonly co-morbid (e.g. sensory motor type, hoarding) with the tic disorders, whereas other OCD symptoms are not (e.g. contamination obsessions and compulsions).[60] Both tic disorders and OCD have a childhood onset, but adult onset OCD (>18 years) is not uncommon,[61,62] while adult onset for the idiopathic tic disorders is rare[47] and exclusionary. The tic disorders characteristically have peak severity in childhood and improve into adulthood[36] as do some forms of childhood onset OCD,[63] but some with OCD have persistent and worsening symptoms into adulthood.[63] Family genetic studies suggest higher than expected rates of OCD in families of those with tic disorders[4] and higher than expected rates of tic disorders in families with OCD.[61] Efforts to identify genes for TS and OCD have, however, been largely unsuccessful, and of the positive studies few have been positive for the tic disorders and OCD. Although the tic disorders and OCD likely involve cortical striatal loops, the neuroimaging findings report different patterns of abnormality in these patient groups and suggest the possibility of accounting for the phenomenological differences between the two disorders insofar as tic disorders involve brain regions and circuits consistent with the sensory and motor phenomena[25] while OCD involves brain regions and circuits consistent with the involvement of more complex cognitions and behavior.[64–67] Although co-morbid OCD, anxiety, and depression in tic disorder patients may respond to SRI treatments tics do not, but rather are responsive to dopamine blockers. OCD, however, is often responsive to the SSRIs, but not to monotherapy with antipsychotics. The addition of antipsychotics to SSRIs for treatment refractory OCD may be particularly useful in those with tic disorders, which in turn may reflect the efficacy of dopamine blockers for tic and tic-related OC symptoms (e.g. sensorimotor symptoms). To date treatment studies have not sufficiently evaluated the moderating effect of putative OCD and the tic disorder subtypes to identify those patients who either respond well or not to SSRIs or antipsychotics. Although behavioral treatments can be effective for both OCD and the tic disorders, their success may be related to their ability to disrupt negative reinforcement patterns that sustain and exacerbate both conditions and may not be due to direct effects on core underlying biological processes.[68] Less is known about other important validators (i.e. biomarkers, temperamental and cognitive and emotional processing vulnerabilities) for the tics disorders and other potential OC spectrum conditions. Finally, an important difference between the tic disorders and OCD is the perception of the two by the public and the medical profession at large. Since Tourette's disorder was first described and especially since the mid 1960s when haloperidol was found to be effective, neurologists have been an important provider group. That tradition has lead to the tic disorders being considered as a neurological disorder by primary care doctors, patients, and patient support groups. Other psychiatric disorders including OCD, although having a clear brain basis, have not been as consistently perceived by the public or nonpsychiatric medical professionals as neurological.

Recommendation: The grouping of the tic disorders needs to reflect scientific commonalities, historical precedent, and future clinical and investigative utility. If the section Disorders First Diagnosed in Infancy, Childhood and Adolescents is retained in DSM-V, then it would be reasonable to keep the tic disorders in this category. Including the tic disorders in a neurodevelopmental disorders category would also be appropriate. Including the tic disorders in a OC Spectrum category is not recommended at this time.

CONCLUSION

Although our understanding of the causes of the tic disorders requires much more research, the cardinal features of the tic disorders have been grounded in a clear understanding of the core phenomenological features (i.e. motor and vocal tics) for over a century. Consistency in diagnostic practice has likely been extremely helpful in the substantial increases in our understanding of the epidemiology, genetics, and neurobiological underpinning of these conditions over the past 30 years.

The goal of this review's recommendation is to maintain the focus on the cardinal features of the tic disorders, to clarify and simplify the diagnostic process, and reduce the use of the TDNOS category. Our recommendation for a common definition of a tic for

all the tic disorders eliminated inconsistency in the definitions in the current DSM. Removing the term "stereotyped" from the definition of a tic reduces the risk of mis-diagnosing tics as stereotypies and vice versa. Simplifying the duration criterion for the tic disorders will likely improve reliability, match current clinical practice, and reduce the number of individuals who will be diagnosed with TDNOS. The addition of new categories for drug-induced tic disorder and tic disorder secondary to medical conditions also will reduce the numbers of individuals diagnosed with TDNOS. The preliminary recommendations for tic disorder diagnostic criteria are presented below with the understanding that the final criteria as published in DSM-V may differ.

PROPOSED CRITERIA FOR THE ADULT AND CHILD ONSET TIC DISORDERS

DSM-V CRITERIA 30X.XX (TOURETTE'S DISORDER)

A. Both multiple motor and one or more vocal tics are present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization).
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. The onset is before 18 years of age.
D. The disturbance is not due to the direct physiological effects of a substance (e.g. cocaine) or a general medical condition (e.g. Huntington's disease or postviral encephalitis).

DSM-V CRITERIA 30X.XX(CHRONIC MOTOR OR VOCAL TIC DISORDER)

A. Single or multiple motor or vocal tic but not both have been present at some time during the illness. (A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization).
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. The onset is before 18 years of age.
D. The disturbance is not due to the direct physiological effects of a substance (e.g. cocaine) or a general medical condition (e.g. Huntington's disease or postviral encephalitis).
E. Criteria have never been met for Tourette's disorder.

Specify:

1. Motor tics only
2. Vocal tics only

DSM-V CRITERIA 30X.XX PROVISIONAL TIC DISORDER

A. Single or multiple motor and/or vocal tics (A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization).
B. The tics have been present for less than 1 year since first tic onset.
C. The onset is before 18 years of age.
D. The disturbance is not due to the direct physiological effects of a substance (e.g. cocaine) or a general medical condition (e.g. Huntington's disease or postviral encephalitis).
E. Criteria have never been met for Tourette's disorder or chronic motor or vocal tic disorder.

DSM-V CRITERIA 30X.XX TIC DISORDER NOT OTHERWISE SPECIFIED

This category is for disorders characterized by tics that do not meet criteria for a specific tic disorder because the movements or vocalizations are atypical in age of onset or clinical presentation.

DSM-V CRITERIA 30X.XX SUBSTANCE-INDUCED (INDICATE SUBSTANCE) TIC DISORDER

A. Motor and/or vocal tics have been present at some time during the illness. (A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization).
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):

1. The symptoms in Criterion A developed during, or within 1 month of, substance intoxication or withdrawal
2. Substance use is etiologically related to the disturbance

DSM-V CRITERIA 30X.XX TIC DISORDER DUE TO A GENERAL MEDICAL CONDITION

A. Motor and/or vocal tics have been present at some time during the illness. (A tic is a sudden, rapid, recurrent, nonrhythmic, motor movement or vocalization).
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

Acknowledgments. We thank TD experts who responded to a survey about the nosology of TS.

REFERENCES

1. Swain JE, Scahill L, Lombroso PJ, et al. Tourette syndrome and tic disorders: a decade of progress. J Am Acad Child Adolesc Psychiatry 2007;46:947–968.
2. Grados MA, Mathews CA. Clinical phenomenology and phenotype variability in Tourette syndrome. J Psychosom Res 2009;67:491–496.
3. CDC. Prevalence of diagnosed Tourette syndrome in persons aged 6–17 years—United States, 2007. MMWR Morb Mortal Wkly Rep 2009;58:581–585.
4. O'Rourke JA, Scharf JM, Yu D, Pauls DL. The genetics of Tourette syndrome: a review. J Psychosom Res 2009;67: 533–545.
5. Church JA, Fair DA, Dosenbach NU, et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. Brain 2009;132:225–238.
6. Raz A, Zhu H, Yu S, et al. Neural substrates of self-regulatory control in children and adults with Tourette syndrome. Can J Psychiatry 2009;54:579–588.
7. Leckman JF, Bloch MH, King RA, Scahill L. Phenomenology of tics and natural history of tic disorders. Adv Neurol 2006; 99:1–16.
8. Mink JW. Clinical review of DBS for Tourette syndrome. Front Biosci (Elite Ed) 2009;1:72–76.
9. Scahill L, Erenberg G, Berlin CM Jr, et al. Contemporary assessment and pharmacotherapy of Tourette syndrome. NeuroRx 2006;3:192–206.
10. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
11. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
12. Diagnostic and Statistical Manual of Mental Disorders. 4th ed, Text Revision DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
13. Freeman RD, Fast DK, Kent M. DSM-IV criteria for Tourette's. J Am Acad Child Adolesc Psychiatry 1995;34:400–401.
14. Erenberg G, Fahn S. Tourette syndrome [Letter to Editor]. Arch Neurol 1996;53:588.
15. Gilles de la Tourette G. La maladie des tic convulsifs. La semaine médicale 1899;19:153–156.
16. ICD-10: The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1990.
17. TSACSG. Definitions and classification of tic disorders. The Tourette Syndrome Classification Study Group. Arch Neurol 1993;50:1013–1016.
18. Freeman RD. Diagnosis and management of Tourette syndrome: practical aspects. Medscape from WebMD; (1997) http://www.medscape.com/viewarticle/431108.
19. Robertson MM, Cavanna AE. The Gilles de la Tourette syndrome: a principal component factor analytic study of a large pedigree. Psychiatr Genet 2007;17:143–152.
20. Storch EA, Murphy TK, Fernandez M, et al. Factor-analytic study of the Yale Global Tic Severity Scale. Psychiatry Res 2007;149:231–237.
21. Mathews CA, Jang KL, Herrera LD, et al. Tic symptom profiles in subjects with Tourette syndrome from two genetically isolated populations. Biol Psychiatry 2007;61:292–300.
22. Alsobrook JP 2nd, Pauls DL. A factor analysis of tic symptoms in Gilles de la Tourette's syndrome. Am J Psychiatry 2002;159: 291–296.
23. Khalifa N, von Knorring AL. Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background. Acta Paediatr 2005;94:1608–1614.
24. Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: Clinical features and longitudinal follow-up. Pediatric Neurology 2008;38:267–272.
25. Harris K, Singer HS. Tic disorders: neural circuits, neurochemistry, and neuroimmunology. J Child Neurol 2006;21:678–689.
26. Knight S, Coon H, Johnson M, et al. Linkage analysis of Tourette syndrome in a large utah pedigree. Am J Med Genet B Neuropsychiatr Genet 2009.
27. TSAICG. Genome scan for Tourette disorder in affected-sibling-pair and multigenerational families. Am J Hum Genet 2007;80: 265–272.
28. TSSG. Tourette Syndrome Study Group Treatment of ADHD in children with tics: a randomized controlled trial. Neurology 2002;58:527–536.
29. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology 2003;60: 1130–1135.
30. Khalifa N, von Knorring AL. Prevalence of tic disorders and Tourette syndrome in a Swedish school population. Dev Med Child Neurol 2003;45:315–319.
31. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28:566–573.
32. Storch EA, Murphy TK, Geffken GR, et al. Reliability and validity of the Yale Global Tic Severity Scale. Psychol Assess 2005;17:486–491.
33. Diniz JB, Rosario-Campos MC, Hounie AG, et al. Chronic tics and Tourette syndrome in patients with obsessive-compulsive disorder. J Psychiatr Res 2006;40:487–493.
34. Pappert EJ, Goetz CG, Louis ED, et al. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology 2003;61:936–940.
35. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics 1998; 102:14–19.
36. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. J Psychosom Res 2009;67:497–501.
37. Coffey BJ, Biederman J, Geller DA, et al. The course of Tourette's disorder: a literature review. Harv Rev Psychiatry 2000;8:192–198.
38. Cook CR, Blacher J. Evidence-based psychosocial treatments for Tic disorders. Clin Psychol Sci Pract 2007;14:252–267.
39. Piacentini JC, Chang SW. Behavioral treatments for tic suppression: habit reversal training. Adv Neurol 2006;99:227–233.
40. Goetz CG, Leurgans S, Chmura TA. Home alone: methods to maximize tic expression for objective videotape assessments in Gilles de la Tourette syndrome. Mov Disord 2001;16:693–697.
41. Freeman RD, Fast DK, Burd L, et al. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol 2000;42:436–447.
42. Lowe TL, Cohen DJ, Detlor J, et al. Stimulant medications precipitate Tourette's syndrome. JAMA 1982;247:1729–1731.
43. Golden GS. The effect of central nervous system stimulants on Tourette syndrome. Ann Neurol 1977;2:69–70.
44. Gadow KD, Sverd J, Sprafkin J, et al. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. Arch Gen Psychiatry 1995;52:444–455.
45. Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. J Am Acad Child Adolesc Psychiatry 1997;36:589–596.
46. Palumbo D, Spencer T, Lynch J, et al. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. J Child Adolesc Psychopharmacol 2004;14:185–194.

47. Chouinard S, Ford B. Adult onset tic disorders. J Neurol Neurosurg Psychiatry 2000;68:738–743.
48. Mejia NI, Jankovic J. Secondary tics and tourettism. Rev Bras Psiquiatr 2005;27:11–17.
49. Singer HS. Discussing outcome in Tourette syndrome. Arch Pediatr Adolesc Med 2006;160:103–105.
50. Rosenberg LA, Brown J, Singer HS. Behavioral problems and severity of tics. J Clin Psychol 1995;51:760–767.
51. Robertson MM, Eapen V, Cavanna AE. The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross-cultural perspective. J Psychosom Res 2009;67:475–483.
52. Santangelo SL, Pauls DL, Goldstein JM, et al. Tourette's syndrome: what are the influences of gender and comorbid obsessive-compulsive disorder? J Am Acad Child Adolesc Psychiatry 1994;33:795–804.
53. Mostofsky SH, Wendlandt J, Cutting L, et al. Corpus callosum measurements in girls with Tourette syndrome. Neurology 1999;53:1345–1347.
54. First MB. 2006. Obsessive Compulsive Spectrum Disorders Conference. http://www.dsm5.org/Research/Pages/ObsessiveCompulsiveSpectrumDisordersConference(June20-22,2006).aspx
55. Ferrao YA, Miguel E, Stein DJ. Tourette's syndrome, trichotillomania, and obsessive-compulsive disorder: how closely are they related? Psychiatry Res 2009;170:32–42.
56. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry 1993;150:98–102.
57. Leckman JF, Walker DE, Goodman WK, et al. "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. American Journal of Psychiatry 1994;151:675–680.
58. Miguel EC, Coffey BJ, Baer L, et al. Phenomenology of intentional repetitive behaviors in obsessive-compulsive disorder and Tourette's disorder. J Clin Psychiatry 1995;56:246–255.
59. Leckman JF, Walker DE, Goodman WK, et al. "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. Am J Psychiatry 1994;151:675–680.
60. Nestadt G, Di CZ, Riddle MA, et al. Obsessive-compulsive disorder: subclassification based on co-morbidity. Psychol Med 2009;39:1491–1501.
61. Samuels JF, Riddle MA, Greenberg BD, et al. The OCD collaborative genetics study: methods and sample description. Am J Med Genet B Neuropsychiatr Genet 2006;141B:201–207.
62. Grant JE, Mancebo MC, Pinto A, et al. Late-onset obsessive compulsive disorder: clinical characteristics and psychiatric comorbidity. Psychiatry Res 2007;152:21–27.
63. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med 2006;160:65–69.
64. Mataix-Cols D, Wooderson S, Lawrence N, et al. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry 2004;61:564–576.
65. Mataix-Cols D, van den Heuvel OA. Common and distinct neural correlates of obsessive-compulsive and related disorders. Psychiatr Clin North Am 2006;29:391–410, viii.
66. Mataix-Cols D, Cullen S, Lange K, et al. Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. Biol Psychiatry 2003;53:482–493.
67. Gilbert AR, Akkal D, Almeida JR, et al. Neural correlates of symptom dimensions in pediatric obsessive-compulsive disorder: a functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 2009;48:936–944.
68. Franklin ME, Himle MB. Evidence-based psychosocial treatments for tic disorders." Theoretical and treatment implications (commentary). Clin Psychol Sci Pract 2007;14:274–278.

Section F .1

Tourette Syndrome

TOURETTE SYNDROME

DAVIDE MARTINO, MD, PHD
NEUROSCIENCE TRAUMA CENTER
BARTS AND THE LONDON SCHOOL OF MEDICINE AND DENTISTRY;
NEUROLOGY DEPARTMENTQUEEN
ELIZABETH HOSPITAL
SOUTH LONDON HNS TRUST
LONDON, UK

JAMES F. LECKMAN, MD
CHILD STUDY CENTER
YALE UNIVERSITY SCHOOL OF MEDICINE
NEW HAVEN, CT

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide.

Oxford New York
Auckland Cape Town Dar es Salaam Hong Kong Karachi
Kuala Lumpur Madrid Melbourne Mexico City Nairobi
New Delhi Shanghai Taipei Toronto

With offices in
Argentina Austria Brazil Chile Czech Republic France Greece
Guatemala Hungary Italy Japan Poland Portugal Singapore
South Korea Switzerland Thailand Turkey Ukraine Vietnam

Oxford is a registered trademark of Oxford University Press
in the UK and certain other countries.

Published in the United States of America by
Oxford University Press
198 Madison Avenue, New York, NY 10016

Library of Congress Cataloging-in-Publication Data
Tourette syndrome / [edited by] Davide Martino, James F. Leckman.
p. ; cm.
Includes bibliographical references and index.
ISBN 978–0–19–979626–7 (hardcover : alk. paper)
I. Martino, Davide. II. Leckman, James F.
[DNLM: 1. Tourette Syndrome. WM 197]
616.8'3—dc23
2012040644

1 3 5 7 9 8 6 4 2
Printed in the United States of America
on acid-free paper

Table of Contents

24

Pharmacological Treatment of Tics

VEIT ROESSNER AND ARIBERT ROTHENBERGER

Abstract

This chapter provides a literature review and a critical commentary of the available evidence on pharmacological treatment of tics in Tourette syndrome (TS). Because of the waxing and waning nature of tics, a meaningful appraisal of treatment efficacy in TS can be given in most cases only after a longer observation time. Environmental or situational factors have a modulating influence on tics, possibly biasing the appraisal of treatment efficacy. Many affected children, adolescents, and adults do not seek or require pharmacological treatment (tic severity: mild to moderate). Nonpharmacological and/or pharmacological interventions make sense for persons with subjective discomfort, social and/or emotional problems, functional interference, etc. The clinical experience is that pharmacotherapy induces faster and probably more prominent tic reduction than behavioral treatment options. The goal of pharmacological treatment is a reduction in tic symptoms. Antipsychotic drugs may produce the most reliable and fastest results, but they also pose the greatest risk of side effects. Risperidone can be considered a first-choice agent for treating tics; pimozide, tiapride, sulpiride, and aripiprazole are regarded as second-choice agents. Clonidine might be helpful mainly in case of TS plus attention-deficit/hyperactivity disorder. For high-quality evidence on pharmacological treatment in TS, future studies should include, for instance, longer observation periods, larger groups, a more standardized methodological approach, placebo controls, a double-blind design, etc.

PATHOPHYSIOLOGY-DRIVEN TREATMENT CONSIDERATIONS

Although the etiology and pathophysiology of tic disorders, including Tourette syndrome (TS),[1] remain unclear (see Chapters 7–15), a dopaminergic hyperfunction is the most consentaneous view as the best target for pharmacological treatment in TS. This is supported not only by neuroscience studies but also by randomized controlled trials (RCTs), as well as the broad clinical experience over the past decades in treating TS with dopamine-blocking agents (Bloch et al., 2011).

So far, genetic studies have not detected clear and easily replicable deviations pointing to abnormalities in one or several neurochemical pathways of patients with TS (see Chapter 7). Nonetheless, clinical medication studies in combination with imaging studies and analyses of human material from cerebrospinal fluid, blood, urine, and postmortem brain tissue in rather small samples resulted mainly in hypotheses on dopaminergic deviances in TS (see Chapters 10 and 13). Studies showing an increased number of striatal and cortical dopamine receptors as well as differences in binding to dopamine transporters in the basal ganglia and release of dopamine following stimulant application leading to tic exacerbation in some patients have further strengthened the hypothesis of an imbalance in the dopaminergic system. Therefore, modulating the dopaminergic metabolism (particularly by blocking the postsynaptic D2 receptors) is the main action of drugs used in the pharmacological treatment of tics.

However, other neurochemical imbalances in TS, such as in the serotoninergic, noradrenergic, cholinergic, glutamatergic, opioid, and

1. The term *Tourette syndrome* (TS) is used to cover all tic disorders.

gamma-aminobutyric acid (GABA)-ergic metabolism, have also been reported (see Chapter 13). Taking into account that those systems function interactively, further studies should look in more detail at these interactions. Nondopaminergic agents, such as selective serotonin reuptake inhibitors (SSRIs) or noradrenergic drugs such as clonidine or atomoxetine, are used with great success in TS plus obsessive-compulsive disorder (OCD) or TS plus attention-deficit/hyperactivity disorder (ADHD) (see Chapter 25 for further details on the treatment of these comorbidities). Such an interaction between neurotransmitter systems is a crucial aspect to address in future research because, particularly due to knowledge gaps on the spectrum of comorbidity and pathophysiology of TS, at present it is difficult to hypothesize which novel pharmacological targets will prove most useful in the near future.

WHAT ARE THE PROBLEMS TO SOLVE WHILE INVESTIGATING THE PHARMACOLOGICAL TREATMENT OF TICS?

In view of this heterogeneous, and as yet incompletely defined, picture of possible pathophysiological deviations in TS with or without comorbid conditions, it is not surprising that there seems to be no imaginable neuropsychopharmacological option that has not been tested in treating tics. Nevertheless, compared to other neuropsychiatric disorders, high-quality evidence on pharmacological treatment of TS remains limited because a good proportion of available studies are far from being flawless in terms of design and methodology. This shortcoming is caused or aggravated by several issues, intrinsically related to TS, that are encountered while investigating treatment effectiveness in this condition.

The problem most specific to TS is the waxing and waning nature of the tics. These intra-individual fluctuations in intensity, frequency, location, complexity, and so forth of tics require longer observation periods to avoid making erroneous conclusions about causality. For example, a therapeutic intervention introduced at the climax of tic severity (date 1 in Fig. 24.1) could be followed by tic reduction. This reduction might be due not to causal mechanisms related to the intervention, but to the natural waxing and waning of the tics. Likewise, a therapeutic intervention at a time point at which tic severity is only mild or moderate (date 2 in Fig. 24.1) could be followed by an increase of TS symptomatology despite its potential to reduce tics. An effective therapeutic intervention might, nonetheless, attenuate the natural waxing of tics. Therefore, in most cases a meaningful appraisal of treatment effectiveness in TS can be made only after longer observation periods (Roessner et al., 2011a). Hence, especially in TS, single-case or case-series observations of pharmacological treatment should be interpreted with extreme caution. This applies all the more as the well-known modulating influence of environmental or situational factors on tics (see Chapters 1, 8, and 14) could bias the intra-individual course of tics with or without pharmacological treatment (e.g., exacerbation during periods of stress, anxiety, excitement, anger, or fatigue; appearance during inquiries about specific movements; reduction during periods of concentration or active engagement). The same holds true for circumscribed situations of rating tic severity within a treatment study.

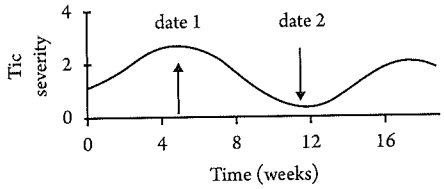

FIGURE 24.1 Evaluation of treatment efficacy in TS in light of its natural waxing and waning course. At date 1 a therapeutic intervention might be followed by tic reduction despite its potential to increase tics or its lack of effect on tics. This must be ascribed not to the causal mechanisms of the intervention but to the natural waxing and waning of the tics. Correspondingly, a therapeutic intervention at date 2 could be followed by an increase of TS symptomatology despite its potential to reduce tics. The therapeutic intervention might attenuate the natural waxing of the tics. Conclusion: Meaningful appraisal of treatment efficacy in TS can be made in most cases only after a longer time.

"NATURAL COURSE" OF TS

In addition to these shorter-term intrinsic, as well as externally triggered, fluctuations, the individual long-term course of tics over years varies within and between individuals. In general, after the period of worst-ever tic severity, occurring between the ages of 7 and 15 years, there is a gradual decline in tic severity (see Chapters 1 and 5). This also implies that adults who still have symptoms severe enough to come to clinical attention are unusual representatives of all subjects who have received a diagnosis of TS, and therefore studies on treatment effectiveness in TS should take this into account. Moreover, future tic severity can be predicted only approximately and not in a precise fashion, although some factors have been identified that correlate with a positive outcome regardless of baseline tic severity (e.g., intelligence, coping and social skills, meaningful daily activities, and good family and social support). Particularly, factors potentially interacting with age and neurotransmitters (e.g., age-related hormonal changes) await more detailed investigation and complicate the determination of whether an agent's primary mechanism of action is directly responsible for its efficacy (see some preliminary considerations on this in Chapter 14).

To date, the reliable measurement of TS severity is a matter of debate (see Chapter 20 for a review of rating instruments). This alone or in combination with the aforementioned aspects results in several problems of decision making related to the commencement, maintenance, or termination of pharmacological treatment, as well as to the design of a treatment study in TS. For example, some pharmacological interventions may be effective only in mild cases, whereas others may show an effect only in patients with more severe tics who have the potential to exhibit improvement across a wider scale. Undoubtedly, the variety of different approaches to assess treatment effectiveness in TS hinders us from making straightforward conclusions based on the available studies. Effectiveness could be defined in one study by the mean improvement in tic frequency or severity, or in terms of the percentage of patients whose symptoms were alleviated, whereas in another study treatment may be considered as effective if it led to a significant reduction of functional impairment. Because recently TS-specific quality-of-life assessment tools have been established, they might be another useful criterion to define treatment effectiveness.

Even more pronounced is the lack of any scientific data concerning the definition and investigation of treatment refractoriness in TS. Particularly, an assessment tool of refractoriness in TS would be of fundamental importance in the process of patient selection for other types of treatment, especially deep brain stimulation (see also considerations in Chapter 26).

Finally, the high rate of comorbid conditions, particularly in the more severely affected patients, could bias trial results on treatment effectiveness. This high rate of comorbid conditions in clinical trial populations is the result of a Berksonian bias (i.e., related to the higher mathematical chance for a patient with two or more coexisting disorders to be referred; referral rate for disorder A + referral rate for disorder B; Banaschewski et al., 2007). As an additional, pertinent example of the relevance of a bias due to comorbidity profile when assessing treatment effectiveness, a meta-analysis by Weisman and colleagues (2012) showed that alpha-2 agonists, including clonidine and guanfacine, were more effective in reducing tic symptoms in patients with TS+ADHD (medium to large effect size = .68), whereas in the absence of comorbid ADHD, the efficacy of these agents was small (effect size = .15) and nonsignificant. Therefore, these authors cautiously question whether this finding indicates a need to refine, or at least reconsider, existing treatment guidelines for TS and other chronic tic disorders, since some of them recognize alpha-2 agonists as the first-line pharmacological treatment for tics due to their more benign safety profile. All these problems not only hamper studies on treatment effectiveness of highest quality, but could also complicate the diagnosis of TS and the way to measure treatment response in individual patients.

DIAGNOSTIC ISSUES PRIOR TO PHARMACOLOGICAL TREATMENT

The above considerations notwithstanding, for the experienced clinician it is usually a simple task to diagnose TS, including in this diagnostic phase also the differentiation of tics from other movement disorders (see Chapters 1 and 17). However, in the context of planning treatment in a TS patient, it is crucial to detect coexisting conditions in order to understand their interplay and to disentangle the contribution of each to the patient's psychosocial impairment in everyday life. This is all the more important because the coexisting conditions often contribute to the patient's overall impairment more than the tics themselves (see Chapters 2–4).

Compared to more dimensionally diagnosed disorders such as ADHD, TS is a quite categorical (tics present/absent) diagnosis. In addition, diagnosing TS does not require functional impairment in the patient. Therefore, it is not surprising that many affected children, adolescents, and even adults with mild to moderate tic severity do not require or even seek pharmacological treatment. This view is supported by an often favorable prognosis that justifies a wait-and-see strategy after an appropriate psychoeducational intervention (see Chapter 22) and reassurance in case of a longer period of tic exacerbation.

Also, there is no evidence that the available pharmacological interventions have any impact on the longer-term prognosis of tics. Therefore, clear criteria are needed to define when the wait-and-see conservative approach should be abandoned and treatment should be initiated.

Such criteria were proposed for the first time in a consensus process within the European clinical guidelines for TS and other tic disorders. (Roessner et al., 2011a). However, there are surprisingly few detailed statements in review articles that would explain the recommendations of the treatment algorithm presented in those guidelines (Fig. 24.2). One reason might be that, to our knowledge, in TS there is no study comparing the effectiveness of different treatment options, such as pharmacological versus behavioral treatment (see Chapter 23) or deep brain stimulation (see Chapter 26). Nevertheless, in the published literature there are some points that could be universally accepted:

- In TS, psychoeducation should be routinely offered to individuals and family members (see Chapter 22).
- The need for compliance by patients and parents and the lack of specially trained therapists and adequate insurance coverage limit the usefulness of habit reversal in clinical routine, although its effectiveness in the context of a multicenter study has recently been reported. The same is true for exposure with response prevention (see Chapter 23).
- In case of treatment refractoriness, combining or switching between different treatment options should be considered.

INDICATIONS FOR ACTIVELY TREATING TS

Nonpharmacological and/or pharmacological interventions should be considered for persons with clear impairment associated with tics, either at first referral or secondary to an exacerbation of symptoms. In particular the following circumstances, especially when persisting for some days, might require initiation of treatment, rather than persisting in the wait-and-see strategy.

Subjective Discomfort (e.g., pain or injury)

Pain in TS may arise from the actual performance of frequent or intense tics causing discomfort by sudden or repeated extreme exertion (e.g., in the head or neck). This kind of pain is usually musculoskeletal, although rare examples of neuropathic pain may occur. Tics can, in rare cases, cause injuries (Krauss & Jankovic, 1996).

> A 13-year-old child was referred to a Pediatric Department with pain in his legs. The pain was relieved by rest and worsened during walking. Physical

examination revealed spontaneous pain in the posterior region of both calves; the Lasegue sign was negative. At admission he had obsessive–compulsive behavior consisting of touching, polydipsia, intrusion of words and phrases, echolalia, poor impulse control, and a complex tic consisting of the need to sit down on his heels abruptly, then rapidly return to a standing position. He had been making this abnormal and marked repetitive movement for one month, many times a day. Obsessive–compulsive disorder and neuropsychiatric behavior had begun 2 years before admission to our hospital; no therapy was given. The child had no previous fractures. No family history of obsessive–compulsive disorder, TS or other neuropsychiatric illness was present. Routine laboratory tests, including antistreptolysin O titers, serum copper and ceruloplasmin, were negative. X-rays of the legs showed a fracture line in the upper third of both peroneal bones, more marked on left side. One month later the leg pain disappeared and the child presented with a simple motor tic (opening his mouth), which spontaneously disappeared some months after onset. Only analgesic treatment was administered. Finally, follow-up radiographs 3 months later showed complete healing of both fractures. (Fusco et al., 2006)

Striking or being struck by a moving body part involved in large-amplitude tics may also cause pain and is sometimes difficult to distinguish from deliberate self-injury. Additionally, some patients obtain relief from tics while experiencing pain, to such an extent that they will deliberately provoke pain to obtain benefit (Riley & Lang, 1989). A smaller number of patients complain of pain associated with the irresistible urge to tic or with aggravating premonitory urges during voluntary efforts to suppress their tics. Some patients report that tics worsen their headaches or migraines. Tic-suppressive medication may in those cases help to reduce the use of pain medication and should thus be considered.

Sustained Social Problems (e.g., social isolation or bullying)

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

Tics do not lead to social impairments in all cases, however, so the issue of social problems needs to be assessed carefully. For example, parents of young children are often exceedingly worried about social problems, whereas adolescents sometimes overestimate the social consequences of their tics, and children in the early elementary grades are often tolerant of tics. When a primary school child becomes socially isolated by his or her peers, coexisting conditions are generally to be blamed more often than tics (Debes et al., 2010). In high school, bullying and social stigmatization due to tics become more common. After proper psychoeducation many children and adolescents will accept their tics and await their natural remission; sometimes, however, medication is indicated to avoid social stigmatization.

Social and Emotional Problems (e.g., reactive depressive symptoms)

In addition to the aforementioned sustained social problems that are a consequence of negative reactions to the social environment, some patients develop depressive and anxious symptoms, low self-esteem, and/or social withdrawal. In those cases, it is not fully clear the extent to which coexisting (sub)clinical symptomatology and self-triggered reactions cause the patient's social and emotional reactions to the tics.

Functional Interference (e.g., impairment of academic achievements)

Functional interference due to tics is relatively rare. However, bouts of tics can interfere with doing homework and falling asleep, and sleep may be disturbed, followed by hypoarousal

during the day. Frequent phonic tics can impair fluency of speech and thus conversations. Moreover, children can expend mental energy in the classroom to suppress their tics, thus reducing their attention to schoolwork and interfering with their academic performance (Kurlan et al., 2001).

CRITERIA FOR SELECTING TREATMENT OPTIONS FOR TS

Compared to behavioral treatment options, pharmacotherapy seems to induce faster and probably more prominent tic reduction. Unfortunately, this observation is purely based on clinical experience and has never been tested in a clinical trial so far. Therefore, it is only possible to indirectly compare effect sizes reported in pharmacological and nonpharmacological studies. This is made even more difficult by the fact that there are few studies on pharmacological, let alone on psychotherapeutic, treatment options that meet rigorous quality criteria. The availability of behavioral therapists with expertise in habit reversal training or exposure with response prevention, as well as possible inadequate insurance coverage (see Chapter 23), also must be considered in treatment planning. For a general treatment algorithm, see Figure 24.2.

Latency and Extent of Treatment Effects

Pharmacological treatment works more quickly than behavioral treatment, so the urgency of reducing tic severity must be taken into consideration in each individual case. The clinician should inform patients and families that the realistic goal of pharmacological treatment in TS should not be to abolish tics, but rather to decrease their number in order to reduce the psychosocial impairment that they have generated. Unrealistic expectations as to the effectiveness of pharmacological treatment of TS will inevitably lead to frustration on the part of the child, the family, and the clinician. Also, the desire for complete tic remission can lead to an unfavorable benefit/risk ratio, causing more problems than the tics themselves. A common example is the "overmedication" of children to the point of excessive daytime sedation or unhealthy weight gain. Families should be informed that medication treatment typically results in only 25% to 50% reduction in tic symptoms.

Clinicians should also be aware of, and inform the family about, the biasing effects of the natural waxing and waning of tics in TS (Fig. 24.1). Hence, the use of formal tic severity rating scales can be recommended to more objectively assess responses to treatment over time. The most precise standardized instrument is the Yale Global Tic Severity Scale (YGTSS), a semistructured interview that records the number, frequency, intensity, complexity, and interference of motor and vocal tics separately (Leckman et al., 1989). In routine clinical practice the Tourette Syndrome Severity Scale (TSSS) can also be used; it is shorter and easier to apply (Shapiro et al., 1988; see Chapter 20 for more details).

Side Effects

The possibility of undesired side effects must be considered, but evidence is quite limited in TS. Most data on side effects of treatment with antipsychotic drugs have been collected in schizophrenic patients, and there is no evidence or at least expert consensus that identical problems could be seen to the same or even a similar extent in persons treated for TS. On average, compared to schizophrenia, the time of titration for antipsychotic agents is shorter and their mean dosage is lower in TS patients. Therefore, the core statements about the side effects of pharmacological treatment cannot be generalized from schizophrenia to TS, partly because there is good evidence that many side effects are dose-related. The incidence of tardive dyskinesia, a long-lasting side effect that does not fully remit even after stopping antipsychotic medication, might be lower in TS, but there are only preliminary data supporting such speculation deduced from clinical experience (Muller-Vahl & Krueger, 2011).

The actual evidence base, as well as clinical experience, indicates that antipsychotic drugs may produce the most reliable and fastest treatment effectiveness, but they also pose the greatest risk of side effects. While the typical

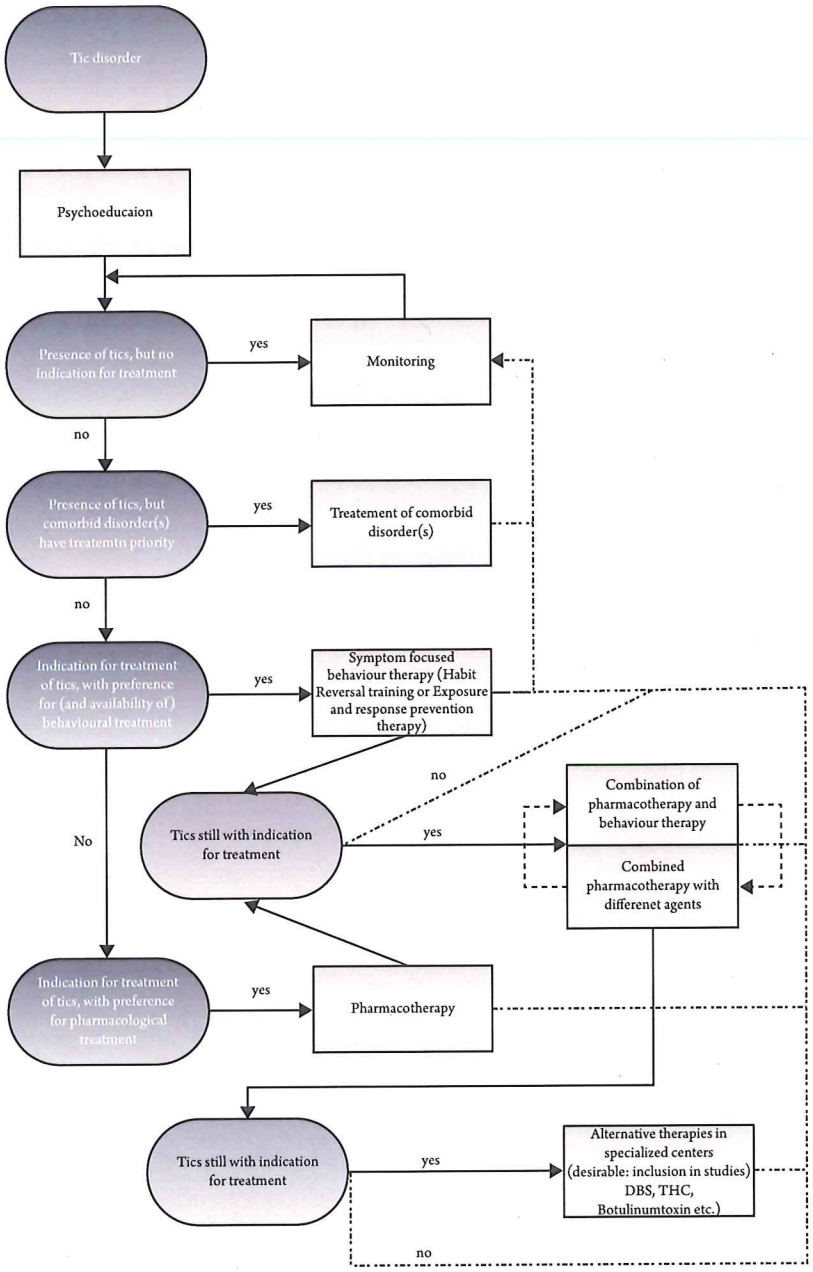

FIGURE 24.2 Decision tree for the treatment of tic disorders, including TS. DBS, deep brain stimulation; THC, tetrahydrocannabinol.

antipsychotic drugs (e.g., haloperidol, pimozide) seem to be somewhat more effective than the newer ones (e.g., risperidone, olanzapine, quetiapine, aripiprazole), they seem to be associated with more and more severe side effects. Also within the group of typical antipsychotic drugs there seem to be differences in the risk of side effects. For example, some studies suggest that pimozide (Sallee et al., 1997) and fluphenazine (Borison et al., 1983) may be as efficacious as haloperidol and produce fewer side effects. Whereas the most common side effects associated with typical antipsychotic drugs are relatively mild and include weight gain and drowsiness,

some patients may experience detrimental effects on cognitive function and/or excessive sedation leading to difficulty in performing cognitive tasks. Additionally, the potential for them to lead to hyperprolactinemia (which is associated with amenorrhea, galactorrhea, and gynecomastia) and extrapyramidal symptoms, such as dystonia, parkinsonism, akathisia, and tardive dyskinesia, must be considered, particularly in view of the remitting "natural" course of tics in many cases. Hyperprolactinemia is reversible, but abnormal movements may persist after the cessation of treatment. Another serious but very rarely reported side effect in TS is the risk of neuroleptic malignant syndrome (Robertson & Stern, 2000).

Although the risk of extrapyramidal side effects may be lower with the atypical antipsychotic drugs, this complication can occur also with these drugs. The anticipated tolerability advantages of the atypical (second- and third-generation) antipsychotic drugs compared with the typical antipsychotics have not been clearly proven because patients treated with these newer drugs also experience side effects usually attributed to the typical antipsychotics, such as weight gain, hyperprolactinemia, sedation, sleep disturbance, and abnormal lipid metabolism. Additionally, newer antipsychotics like ziprasidone have a lower risk of weight gain but have generated concern because of the potential to alter cardiac conduction, especially QTc prolongation. As an alternative to antipsychotic drugs, benzamides seem comparably or only minimally less effective, and their use is much more rarely associated with extrapyramidal side effects. For example, tiapride is even recommended for the treatment of tardive dyskinesia because "clinical studies demonstrate its excellent efficacy in neuroleptic-induced tardive dyskinesia, [...] tiapride is well tolerated, [...] and adverse events are generally rare and mild" (Dose & Lange, 2000). "Typical" side effects of antipsychotic drugs, such as weight gain, hyperprolactinemia, and sedation, were seen during treatment of TS with benzamides, but in a less severe form and in fewer patients.

New analyses have questioned the effectiveness of alpha-2 agonists, including clonidine and guanfacine, in reducing tic symptoms (Weissman et al., submitted). Both agents have the advantage of a lower risk of side effects. The main side effects of clonidine are sedation and hypotension. Guanfacine is generally preferred over clonidine because it tends to cause less sedation and hypertension. Moreover, it acts longer than clonidine and therefore fewer daily doses are needed. Periodic blood pressure monitoring is advised during use, particularly because of possible rebound hypertension associated with abrupt discontinuation (Jankovic & Kurlan, 2011).

PHARMACOLOGICAL TREATMENT OPTIONS FOR TS

Although many drugs have been tested in single cases or case series of TS patients, there has not been much improvement in terms of evidence since the statement by Robertson and Stern (2000) that "the treatment of the Gilles de la Tourette syndrome has evolved from case reports, clinical experience and more recently blinded trials usually in small numbers of patients." This lack of high-quality studies is reflected by the fact that haloperidol is still the only drug that has been approved for TS widely in the world. Nevertheless, haloperidol is today usually not a drug of first choice in clinical practice because of its side effects. Additionally, the insufficient base of evidence results in a very heterogeneous and somewhat confusing situation of several available review publications presenting, at least in part, divergent recommendations on pharmacological treatment options for TS. In the past 2 years, six new general reviews have been published that included at least one section on pharmacological treatment of TS (Du et al., 2010; Eddy et al., 2011; Jankovic & Kurlan 2011; Kimber, 2010; Kurlan, 2010; Rickards, 2010) and three reviews have been dedicated to the pharmacological treatment of TS (Bestha et al., 2010; Parraga et al., 2010; Singer, 2010). The recommendations given by each of these groups reflect their individual clinical experience and tradition and therefore are highly diverse. For example, two U.S. TS experts (Jankovic & Kurlan, 2011) favor guanfacine and tetrabenazine, whereas the

German experts recommend the benzamide tiapride as first-line medication (Rothenberger et al., 2007). Both these recommendations are not based on best evidence from available RCTs. In addition to the agent selection, the selection of the outcomes differs between the reviews. For example, Singer (2010) gives very detailed and helpful, but mainly experience-driven, suggestions about dosing and dosage, whereas Eddy and colleagues (2011) give dosage information for only some of the included agents without explaining the selection criteria for this information. Jankovic and Kurlan (2011) did not report any information on dosage in their more general review on TS, although they recommended first- and second-line agents. Such a more subjective than systematic selection of recommended agents and associated outcome parameters in the existing reviews further emphasizes the need of well-designed RCTs in TS that could provide results of comparable methodological quality.

HIGH EVIDENCE BY COCHRANE REVIEWS

For their Cochrane review, Pringsheim and Marras (2009) identified six RCTs that used pimozide in TS (total 162 participants, age range 7–53 years). Pimozide was compared to placebo (one trial), haloperidol (one trial), placebo and haloperidol (two trials), and risperidone (two trials). The authors concluded that pimozide reduced tics more effectively than placebo. However, it was slightly less effective than haloperidol, while it showed fewer side effects. In terms of tic reduction or side effects, the two studies comparing pimozide and risperidone found no significant differences between the agents.

Pierce and Rickards (in press) screened the literature for all randomized, controlled, double-blind studies comparing atypical antipsychotics to placebo for the treatment of tics in TS. Because neither of the above-mentioned trials using risperidone included a control group receiving placebo, they did not include those studies in their Cochrane review. Parallel-group and crossover studies of children or adults, at any dose and for any duration, were included. The authors identified only three randomized placebo-controlled trials, two comparing risperidone and one ziprasidone with placebo. In one trial risperidone was much more effective than placebo, although the 95% confidence intervals were large. The remaining two trials did not reveal a statistically significant superiority of treatment with risperidone or ziprasidone respectively compared to placebo. In particular, risperidone caused several extrapyramidal side effects and weight gain.

The third Cochrane review (Curtis et al., 2009) analyzed the effectiveness of delta-9-tetrahydrocannabinol (delta-9-THC) in the treatment of TS. A total of 28 different patients included in one double-blind, parallel-group trial and in one double-blind, crossover trial were studied. Although both trials reported a positive effect of delta-9-THC, the improvements in tic frequency and severity were small and apparent only on selected outcome measures.

In summary, all three Cochrane reviews on the pharmacological treatment of TS (Curtis et al., 2009; Pierce & Rickards, in press; Pringsheim & Marras, 2009) came to the conclusion that this very small and heterogeneous base of evidence not only for the effectiveness but also for the safety of potential drugs does not allow firm evidence-based recommendations to be made. The actual evidence based on RCTs not included in these Cochrane reviews is also alarmingly limited. An overview of all existing RCTs in TS (double-blind, placebo-controlled or comparator, parallel-group or crossover study) is presented in Table 24.1.

Therefore, broad clinical experience is still guiding both consensus findings of experts in terms of the pharmacological treatment of tics and the individual treatment decisions of clinicians.

SELECTED AGENTS

For a comprehensive review of the existing evidence on pharmacological treatment of TS, please see Roessner and colleagues (2011a). In the following section of the chapter, we present information about the agents that are most often

Table 24-1. Overview of All RCTs on TS that Represent Double-Blind, Placebo-Controlled or Comparator, Parallel-Group or Crossover Studies

MEDICATION	DESIGN	N; MEAN AGE (SD); RANGE; SEX[a]	DRUG DOSE[b]	REFERENCE
Alpha-Adrenergic Agonists				
Clonidine	Randomized, double-blind, parallel group, comparator: risperidone	Clonidine: 12; 12.1 (3.0); 7–17; 11 males, 1 female Risperidone: 9; 10.4 (2.7); 7–17; 8 males, 1 female	Clonidine: 0.005 mg/kg/d (highest) or 0.350 mg/d over 3–4 weeks (with a minimum target dose of 0.0025 mg/kg/d) Risperidone: 0.06 mg/kg/d (highest) with a minimum target dose of 0.03 mg/kg/d	Gaffney et al., 2002
	Randomized, double-blind, placebo-controlled parallel	Clonidine: 326; 10.5 (2.82); 6–18; 270 males, 56 females Placebo: 111; 9.89 (2.77); 6–18; 96 males, 15 females n = 6 dropouts	Clonidine: 1–2 mg/week Placebo	Du et al., 2008
Guanfacine	Randomized, double-blind, placebo-controlled, parallel group	34; 10.4 (2.01); 7–14; 31 males, 3 females Guanfacine: n = 17 Placebo: n = 17	Guanfacine: 1.5–3.0 mg/d Placebo	Scahill et al., 2001
	Randomized, double-blind, placebo-controlled parallel	Guanfacine: 12; 9.5 (2.0); 6–16; 12 males, 0 females Placebo: 12; 11.3 (2.4); 6–16; 8 males, 4 females	Guanfacine: initial dose: 0.5 mg/d; 1.0 mg/ b.i.d (highest) Placebo	Cummings et al., 2002

(Continued)

Table 24-1. (Continued)

MEDICATION	DESIGN	N; MEAN AGE (SD); RANGE; SEX[a]	DRUG DOSE[b]	REFERENCE
Typical Neuroleptics				
Haloperidol	Randomized, double-blind, placebo-controlled, parallel Comparator: pimozide	9; 18.7; 8–28; 7 males, 2 females	Haloperidol: initial dose: 2 mg/d; 12 mg/d (highest) Pimozide: initial dose: 2 mg/d; 12 mg/d (highest) Placebo	Ross & Moldofsky, 1978
	Randomized, double-blind, placebo-controlled parallel and crossover design Comparator: pimozide	57; 21.1 (11.0); 8–46; 44 males, 13 females Haloperidol: n = 18 Pimozide: n = 20 Placebo: n = 19	Haloperidol: 2–20 mg/d Pimozide: 2–48 mg/d Placebo	Shapiro et al., 1989
	Randomized, double-blind, placebo-controlled, double-crossover Comparator: pimozide	22; 10.2 (2.5); 7–16; 17 males, 5 females	Haloperidol: 3.5 mg/d (mean) Pimozide: 3.4 mg/d (mean) Placebo	Sallee et al., 1997
Pimozide	Randomized, double-blind, placebo-controlled, parallel Comparator: haloperidol	9; 18.7; 8–28; 7 males, 2 females	Pimozide: initial dose: 2 mg/d; 12 mg/d (highest) Haloperidol: initial dose: 2 mg/d; 12 mg/d (highest) Placebo	Ross & Moldofsky, 1978

Randomized, double-blind, placebo-controlled parallel and crossover design Comparator: haloperidol	57; 21.1 (11.0); 8–46; 44 males, 13 females Pimozide: n = 20 Haloperidol: n = 18 Placebo: n = 19	Pimozide: 2–48 mg/d Haloperidol: 2–20 mg/d Placebo	Shapiro et al., 1989
Randomized, double-blind, placebo-controlled, double-crossover Comparator: haloperidol	22; 10.2 (2.5); 7–16; 17 males, 5 females	Pimozide: 3.4 mg/d (mean) Haloperidol: 3.5 mg/d (mean) Placebo	Sallee et al., 1997
Randomized, double-blind, parallel group Comparator: risperidone	Pimozide: 24; 23.5 (median); 11–45; 21 males, 3 females Risperidone; 26; 20.0 (median); 11–50; 23 males, 3 females n = 9 dropouts	Pimozide: 2.9 mg/d (mean); range 1–6 mg/d Risperidone: 3.8 mg/d (mean); range 0.5–6 mg/d	Bruggeman et al., 2001
Randomized, double-blind, crossover Comparator: risperidone	19; 11 (2.5); 7–17; 15 males, 4 females n = 6 dropouts	Pimozide: 1–4 mg/d; 2.4 mg/d (mean) Risperidone: 1–4 mg/d; 2.5 mg/d (mean) Placebo for 2 weeks before pimozide/risperidone	Gilbert et al., 2004
(Randomized ?), double-blind, crossover Comparator: olanzapine	4; 28.5; 19–40; 4 males, 0 females	Pimozide: 2 and 4 mg/d Olanzapine: 5 and 10 mg/d	Onofrj et al., 2000

(Continued)

Table 24-1. (Continued)

MEDICATION	DESIGN	N; MEAN AGE (SD); RANGE; SEX[a]	DRUG DOSE[b]	REFERENCE
Atypical Neuroleptics				
Olanzapine	(Randomized ?), double-blind, crossover Comparator: pimozide	4; 28.5; 19–40; 4 males, 0 females	Olanzapine: 5 and 10 mg/d Pimozide: 2 and 4 mg/d	Onofrj et al., 2000
Risperidone	Randomized, double-blind, placebo-controlled, parallel group	34; 19.8 (17.01); 6–62; 30 males, 4 females Risperidone: n = 16 Placebo: n = 18	2.5 ± 0.85 mg/d (mean) Placebo	Scahill et al., 2003
	Randomized, double-blind, placebo-controlled, parallel group	Risperidone: 23; 31 (median); 17–49; 19 males, 4 females Placebo: 23; 33 (median); 14–45; 17 males, 6 females	Risperidone: 2.5 mg/d (mean); range 1–6 mg/d Placebo	Dion et al., 2002
	Randomized, double-blind, parallel group Comparator: clonidine	Risperidone: 9; 10.4 (2.7); 7–17; 8 males, 1 female Clonidine: 12; 12.1 (3.0); 7–17; 11 males, 1 female	Risperidone: 0.06 mg/kg/d (highest) (with a minimum target dose of 0.03 mg/kg/d) Clonidine: 0.005 mg/kg/d (highest) or 0.350 mg/d over 3–4 weeks (with a minimum target dose of 0.0025 mg/kg/d)	Gaffney et al., 2002
	Randomized, double-blind, parallel group Comparator: pimozide	Risperidone; 26; 20.0 (median); 11–50; 23 males, females Pimozide: 24; 23.5 (median); 11–45; 21 males, 3 females n = 9 dropouts	Risperidone: 3.8 mg/d (mean); 0.5–6 mg/d Pimozide: 2.9 mg/d (mean); range 1–6 mg/d	Bruggeman et al., 2001

	Randomized, double-blind, crossover Comparator: risperidone	19; 11 (2.5); 7–17; 15 males, 4 females n = 6 dropouts	Risperidone: 1–4 mg/d; 2.5 mg/d (mean) Pimozide: 1–4 mg/d; 2.4 mg/d (mean)	Gilbert et al., 2004
Ziprasidone	Randomized, double-blind, placebo-controlled, parallel group	Ziprasidone: 16; 11.3; 7–14; 14 males, 2 females Placebo: 12; 11.8; 8–16; 8 males, 4 females n = 4 dropouts	Ziprasidone: 28.2 ± 9.6 mg/d (mean); range 5–40 mg/d Placebo	Sallee et al., 2000
Benzamides				
Sulpiride	Randomized, double-blind, placebo-controlled, crossover Comparator: fluvoxamine	Sulpiride: 5; 29.6 (2.9); 3 males, 3 females Fluvoxamine: 6; 28.3 (3.2); 5 males, 1 female	Sulpiride: 0.2 g–1 g/d Fluvoxamine: 50–300 mg/d Placebo	George et al., 1993
Tiapride	Randomized, double-blind, placebo-controlled, crossover	n = 17	Tiapride: 6 mg/kg/d Placebo	Eggers et al., 1988

(Continued)

Table 24-1. (Continued)

MEDICATION	DESIGN	N; MEAN AGE (SD); RANGE; SEX[a]	DRUG DOSE[b]	REFERENCE
Baclofen	Randomized, double-blind, placebo-controlled, crossover	10; 11.7 (2.9); 8–14; 7 males, 3 females n = 1 dropout	Baclofen: 20 mg t.i.d Placebo	Singer et al., 2001
Botulinum toxin	Randomized, double-blind, placebo-controlled, crossover	20; 31.5; 15–55; 13 males, 5 females n = 2 dropouts	Treatment was with variable doses of botulinum toxin A (Botox; Allergan, Canada). Placebo	Marras et al., 2001
Fluvoxamine	Randomized, double-blind, placebo-controlled, crossover Comparator: sulpiride	Fluvoxamine: 6; 28.3 (3.2); 5 males, 1 female Sulpiride: 5; 29.6 (2.9); 3 males, 3 females n = 6 dropouts	Fluvoxamine: 50–300 mg/d Sulpiride: 0.2–1 g/d Placebo	George et al., 1993
Levetiracetam	Randomized, double-blind, placebo-controlled, crossover	22; 12.2 (2.3); 8–16; 21 males, 1 female n = 2 dropouts	Levetiracetam: initial dose: 10 mg/kg/d; 30 mg/kg/d (highest) Placebo	Smith-Hicks et al., 2007
Nicotine	Randomized, double-blind, placebo-controlled, (probably) crossover	23; 12.0 (2.8); 8–17; 19 males, 4 females n = 9 dropouts	Nicotine: 7 mg/d Placebo	Howson et al., 2004

Talipexole	Randomized, double-blind, placebo-controlled, crossover	13; 39.2; 19–63; 13 males, 0 females n = 5 dropouts	Talipexole: initial dose: 0.3 mg/d; 2.4 mg/d (highest) Placebo	Goetz et al., 1994
Tetrahydro-cannabinol	Randomized, double-blind, placebo-controlled, crossover	12; 34 (13); 18–66; 11 males, 1 female	THC: 5–10 mg/d Placebo	Muller-Vahl et al., 2002
	Randomized, double-blind, placebo-controlled parallel	24; 33 (11); 18–68; 19 males, 5 females THC: n = 12 Placebo: n = 12 n = 7 dropouts	THC: 10 mg/d Placebo	Muller-Vahl et al., 2003
Topiramate	Randomized, double-blind, placebo-controlled, parallel	29; 16.5 (9.89); 7–65; 26 males; 3 females Topiramate: n = 15 Placebo: n = 14 n = 9 dropouts	Topiramate: 118 mg/d (mean) Placebo	Jankovic et al., 2010

[a] Not all data are available for each study. [b] Drug dose in mg/kg of body weight/day if available, otherwise in mg/day (mg/d); standard drug dose if available, otherwise mean drug dose if available, otherwise highest dose.

used and that have been intensively investigated and commonly mentioned. The order of the selected agents is arbitrary in both the text and in Tables 24.1 and 24.2, and does not reflect a recommendation or level of evidence. For a tentative attempt at recommendations, see the conclusions section of the chapter.

Noradrenergic Agents

In general, particularly U.S. experts favor the two alpha-2 adrenergic agonists clonidine and guanfacine as first-line treatment for mild to moderate tics (Singer, 2010). Such regional preferences seem to largely reflect differences in regional drug supply and experience (Jankovic & Kurlan, 2011; Muller-Vahl & Roessner, 2011). The tic-suppressing effects of both alpha-2 adrenergic agonists seem to be generally smaller, however, than those of antipsychotic agents (Robertson, 2000), although a small, single-blind, randomized trial showed similar effectiveness of clonidine and risperidone (Gaffney et al., 2002). The treatment effectiveness of clonidine and guanfacine is a good example of the large gaps of sufficiently qualitative evidence on the pharmacological treatment of TS (Weisman et al., 2012).

Although clonidine has been used for nearly three decades in the treatment of TS, there are only a few controlled studies supporting its use. At present, a transdermal clonidine patch is available that can be applied once weekly; however, it was found to cause local skin irritation and problems related to displacement (Du et al., 2008). Side effects of clonidine include sedation, irritability, dizziness, dry mouth, headache, orthostatic hypotension, dysphoria, and sleep disturbance. Although many authors report that these side effects are mild and usually self-limiting, this view is not fully supported, especially when moderate to severe tics require higher dosage. The initial dose of clonidine is 0.05 mg orally at bedtime. Because of its short half-life (about 6 hours), some suggest a more frequent dosage schedule for tics, and definitely for ADHD, than the usually recommended twice-a-day regimen. The maximum dose should not exceed 0.3 to 0.4 mg per day.

Guanfacine has also shown only modest effectiveness in reducing tics, with inconsistencies across studies of different quality and on heterogeneous clinical samples. The often-cited suggestion that guanfacine is better tolerated than clonidine requires caution because there has been no direct comparison study conducted between the two agents (Sandor, 2003). The main side effects of guanfacine are dizziness, drowsiness, confusion, fatigue, headache, hypotension, and mental depression. Constipation and dry mouth are common. Guanfacine, previously approved to treat hypertension in several European countries, has been withdrawn from the market in several of these countries. Guanfacine should be started at a dosage of 0.5 mg at bedtime and should be increased by 0.5 mg every 5 to 7 days, if necessary, to a maximum dose of 4 mg per day in a once-a-day or twice-a-day regimen.

For the selective noradrenergic reuptake inhibitor atomoxetine, the situation is quite similar to that for guanfacine. Atomoxetine was originally developed by Eli Lilly as a treatment for depression. Due to its unfavorable benefit/risk ratio in these trials, it was approved in late 2002 for ADHD. It was shown to be effective in randomized, placebo-controlled trials for ADHD in children, including patients with coexisting mild to moderate tics. As a result of its different mechanism of action, many patients who previously did not respond to stimulants have shown some response to atomoxetine (see Chapter 25). Common adverse effects of atomoxetine include nausea, emesis, diminished appetite, and insomnia. TS-specific doses have not been identified; hence, 0.5 to 1.2 mg per kg body weight could be seen as the optimal therapeutic range.

Antipsychotic Agents

During the past 40 years positive treatment effects in TS have regularly been reported for D2 dopamine receptor blockers (on average a marked decrease of tics in about 70% of cases; Shapiro & Shapiro, 1998). Although the blockade of striatal D2 dopamine receptors is thought to lead to reduction of tics, a high blockade of the receptors commonly correlates with the rate

of unfavorable side effects, such as extrapyramidal symptoms or tardive dyskinesia (Bressan et al., 2004)—although it has been observed that the risk of tardive dyskinesia might be lower in TS (Muller-Vahl & Krueger, 2011).

TYPICAL ANTIPSYCHOTICS

The typical antipsychotics haloperidol and pimozide were the first ones shown to be effective in placebo-controlled treatment studies in TS. Although slight differences in effectiveness, as well as the rate and severity of side effects, were reported in available trials, no firm conclusions should be drawn. Several limitations and the small number of studies result in heterogeneity of findings. In a double-blind, 24-week, placebo-controlled, randomized double-crossover study of the most commonly used doses of haloperidol (mean dose 3.5 mg per day) and pimozide (mean dose 3.4 mg per day) conducted in 22 subjects aged 7 to 16 years, pimozide was significantly more effective than placebo in reducing tics, whereas haloperidol failed to have a significant effect, possibly due to the limited study power. Moreover, haloperidol exhibited a threefold higher frequency of serious side effects and significantly greater extrapyramidal symptoms than pimozide (Sallee et al., 1997).

The high frequency of side effects such as drowsiness, movement disorders (i.e., dystonia, akathisia, and pseudoparkinsonism, probably due to the strong dopaminergic blockade in the nigrostriatal pathways), anxiety, increased appetite, and hyperprolactinemia (with its complications such as gynecomastia, galactorrhea, irregular menses, and sexual dysfunction) limits the use of the typical antipsychotics at higher doses. In daily clinical practice, lower doses such as 1 to 4 mg per day for haloperidol and 2 to 8 mg per day for pimozide in divided doses are typically used today to treat TS. Doses above 5 mg per day for haloperidol and 10 mg per day for pimozide should be avoided.

ATYPICAL ANTIPSYCHOTICS

Like typical antipsychotics, atypical antipsychotics were found to be effective in the treatment of TS. We will review the most commonly used atypical antipsychotics in order of approval by the U.S. Food and Drug Administration (for non-TS indications).

Risperidone (FDA approval in 1993) is the atypical antipsychotic agent with the broadest base of evidence concerning the treatment of TS, which includes randomized, double-blind, placebo-controlled trials. Although similarly effective as haloperidol and pimozide in reducing tics, risperidone showed less frequent and less severe side effects. The most common side effects were mild to moderate sedation, fatigue, and somnolence, hypotension, metabolic adverse reactions (glucose and lipid metabolism), and hyperprolactinemia, which subsequently resolved with continued administration of the medication or with a dose reduction. Very rarely, clinically significant extrapyramidal symptoms have been observed. Weight gain as a consequence of increased appetite should be considered and, if necessary, suitable interventions started. The mean daily dose of about 2.5 mg (range 1–6 mg/day) should be given on a twice-a-day regimen.

For olanzapine (FDA approval in 1996), there are only some case reports and open-label studies suggesting effectiveness in the treatment of TS. Interestingly, in contrast to the other atypical antipsychotics, no European expert recommended olanzapine based on response to a survey questioning which medication expert clinicians would consider first, second, and third treatment choices (Roessner et al., 2011b). The side effects are very similar to those of risperidone, although olanzapine seems associated with a lower incidence of hyperprolactinemia and more severe weight gain. After starting with 2.5 mg orally every evening, a gradual escalation to 5 to 10 mg per day in divided doses, according to individual requirements, should be pursued. Maximum daily dose is 20 mg.

Evidence about TS treatment with quetiapine (FDA approval in 1997) is similarly very limited. Few reports document side effects with this drug during treatment of TS, but they seem to be less severe and frequent than those observed with other atypical antipsychotics. After initial dosing with 25 to 50 mg per day, quetiapine

may be increased, as tolerated, to relatively high doses, up to 600 mg daily in two divided doses.

Only one randomized, double-blind, placebo-controlled study (Sallee et al., 2000) and one open-label study have shown effectiveness of ziprasidone (FDA approval in 2001) in reducing tics. The side effects were very mild and included sedation, weight gain, and hyperprolactinemia. Different dose recommendations are present in the literature; the usual range is 5 to 40 mg per day in divided doses.

Compared to olanzapine, quetiapine and ziprasidone, aripiprazole (FDA approval in 2002) has been studied much more extensively in TS and has shown a very promising benefit/risk ratio (Wenzel et al., 2012). A randomized, double-blind, placebo-controlled study is, however, still lacking. Even in "refractory" TS, aripiprazole has shown good effectiveness. It seems reasonably well tolerated; the most common adverse reactions include nausea, akathisia, weight gain, and sedation. As a starting dose 2 to 2.5 mg per day is often reported; the maximum dose is 30 mg per day.

BENZAMIDES

Two agents belonging to this family of drugs, tiapride and sulpiride, are used in the treatment of TS, although mainly in Europe (Roessner et al., 2011a). Despite its selective D2 dopamine receptor antagonism, these molecules have a low (sulpiride) or virtually absent (tiapride) antipsychotic effect compared to the typical antipsychotics, with fewer extrapyramidal and autonomic side effects than haloperidol. After early reports of success in treating TS with tiapride in the 1970s, only a few placebo-controlled studies with small sample sizes have been published. Nevertheless, due to its favorable benefit/risk ratio, tiapride still represents the recommended first-line treatment of tics in some European countries, such as Germany (Rothenberger et al., 2007). Its main side effects are drowsiness, moderate transient hyperprolactinemia, and weight gain (mean weight gain was 2–4 kg [Meisel et al., 2004] at a dose range of 100–900 mg per day). Tiapride has no impact on cognitive performance or neurophysiological recordings such as EEG frequency analysis and sensory evoked potentials in children. The neurosecretory, hypothalamic-hypophyseal regulation of the sex hormones, thyroid stimulating hormone, growth hormone, or thyroid hormone, moreover, is not disturbed by tiapride. Likewise, positive effects of sulpiride on tics have been reported regularly since the 1970s (Robertson & Stern, 2000). In addition to its mild antipsychotic action, an antidepressant and anxiolytic effect has been observed with low doses of sulpiride; in addition, it seems to have positive effects on obsessive-compulsive symptoms co-occurring with tics as well as on OCD without tics. The most common side effects of sulpiride include sedation, drowsiness (in up to 25% of cases), and, less frequently, paradoxical depression; a few patients also complained of restlessness and sleep disturbances. Another important problem with sulpiride is the strong stimulation of prolactin secretion, causing galactorrhea/amenorrhea and a commonly observed increase of appetite leading to weight gain. Other side effects (hypotension, rarely long-QT syndrome, dry mouth, sweating, nausea, activation or sedation, insomnia, allergic rash, or pruritus) are rare. The titration of tiapride and sulpiride starts with a dose of 50 or 100 mg (2 mg per kg body weight) per day, and the dosage should not exceed 2 to 10 mg per kg body weight. Particularly at higher doses a division into three daily doses might be helpful.

Alternatives

Tetrabenazine for the treatment of TS has been discussed in previous reviews, especially by U.S. authors (Jankovic & Kurlan, 2011; Kurlan, 2010). This compound acts as a vesicular monoamine transporter type 2 inhibitor by depleting presynaptic dopamine and serotonin stores and by blocking postsynaptic dopamine receptors. Therefore, tetrabenazine might be an alternative to antipsychotic treatment due its divergent mechanism of action resulting in different efficacy and adverse reactions profiles compared to antipsychotics. However, even compared to the generally low level of evidence for other TS treatment options, very few clinical studies on hyperkinetic movement disorders are

available with this drug, including small clinical samples of TS patients and two retrospective chart reviews. Possible side effects of tetrabenazine include drowsiness/fatigue, nausea, depression, parkinsonism, and akathisia, but all these side effects resolve with reduction of daily dosage. Weight gain seems to be less pronounced at doses of comparable anti-tic efficacy in respect to antipsychotics, and most patients who switched from an antipsychotic drug to tetrabenazine subsequently lost weight. The usual effective dose is 50 to 150 mg per day divided into three daily doses, with a maximum recommended dose of 200 mg per day.

The benzodiazepine clonazepam, which acts primarily on the GABAergic system, has a long history in the treatment of TS. It is included in many reviews *inter alia* due to its rapid onset of tic reduction. Only a few open-label and single-blind studies of clonazepam in TS have been carried out. In a single-blind comparison with clonidine in 20 children, clonazepam was superior in suppressing tics (Drtílková, 1996). As with all benzodiazepines, tolerance and side effects including sedation, short-term memory problems, ataxia, and paradoxical disinhibition often limit the use of clonazepam (Goetz, 1992). Clonazepam has been used at doses up to 6 mg per day to treat TS.

All of the aforementioned agents have systemic effects. Alternatively, botulinum toxin injections are used to treat persistent well-localized (noncomplex) motor and, sometimes, vocal tics by temporarily weakening the associated muscles. Since the 1990s, only case reports and case series of botulinum toxin treatment in TS have been published. The only exception is a randomized, double-blind, controlled clinical trial showing that the tic frequency and the premonitory urge were reduced by botulinum toxin injection (Marras et al., 2001). Yet patients subjectively perceived this treatment as overall not effective in improving their condition, perhaps because only a selected subset of tics can be addressed by local botulinum toxin injections. Side effects include temporary soreness, mild muscle weakness, and hypophonia when vocal tics are treated with vocal cord injections.

Additional treatment alternatives for TS in children have been used experimentally, for example dopamine agonists such as pergolide and ropinirole. Pergolide is a mixed D_1-D_2-D_3 dopamine receptor agonist. A study with 57 children showed that a low-dose treatment with pergolide (0.15–0.45 mg per day), compared to placebo, led to a significant improvement in tic severity (Gilbert et al., 2003). Likewise, in an open-label trial tic severity decreased in 75% of patients (24/32) during treatment with small doses of pergolide (0.1–0.3 mg per day). Side effects were relatively harmless and extrapyramidal side effects were absent (Lipinski et al., 1997). There are only a few studies on treatment effects of the dopamine agonist ropinirole. It does not interact with D1 receptors but has a high selectivity for D3 receptors and a weaker affinity for D2 receptors. The effectiveness of ropinirole at a dose of 0.25 to 0.5 mg twice a day was shown in a study with 15 patients (mean age 28.1 ± 6.1 years); of these, 10 reported a significant improvement in tic severity and frequency (Anca et al., 2004).

Antiandrogens such as finasteride and flutamide have also been tested in TS. Because of the preponderance of males affected by TS, androgens may possess a key role in its pathophysiology. During treatment with finasteride, patients displayed a reduction in total, motor, and phonic tics. Only 2 of 10 patients complained of a decline in libido and occasional difficulty in achieving erection (Muroni et al., 2011). A double-blind, placebo-controlled, crossover trial of flutamide (13 adults [10 men and 3 women]) showed a decrease in motor but not phonic tic severity, but the effects were relatively small in magnitude. Although subjects generally tolerated well a flutamide dose of 750 mg per day, this medication has caused in other conditions severe (sometimes fatal) liver dysfunction, in addition to a number of less severe but troublesome side effects such as diarrhea and gastric discomfort (Peterson et al., 1998).

CONCLUSIONS

There are unfortunately few studies on the pharmacological treatment of TS that fulfill high

methodological standards. There are also very few studies directly comparing the effectiveness of different psychopharmacological agents, foremost with regard to longer-term effects or in cases refractory to previously tried medications. This has led to different recommendations in the literature, which depend heavily upon the authors' personal experiences and preferences. The question of the effectiveness of polypharmacy is another area in which evidence-based knowledge is virtually absent, even though it is not rare for clinicians to resort to polypharmacological treatment when dealing with treatment-refractory patients in their routine practice.

Based on the available, albeit insufficient, evidence base, as well as on experts' experience and preferences, risperidone can be recommended as a first choice for the treatment of tics. Side effects represent its biggest limitation, primarily weight gain and sedation. Pimozide has relatively good evidence, with a better adverse reaction profile than haloperidol. Tiapride and sulpiride can be recommended based on the broad clinical experience and favorable adverse reaction profile, although more controlled clinical studies are urgently required to prove this. Aripiprazole has great potential, especially in the treatment of refractory cases and probably less pronounced risk of severe weight gain. Finally, clonidine can be administered, especially when coexisting ADHD is present. All the other agents mentioned in Table 24.2 may be considered as alternatives, once the response to one or more of these medications has been unsatisfactory.

To overcome the dearth of high-quality evidence on pharmacological treatment in TS, all three available Cochrane reviews, as well as many experts on TS, urgently advocate for future trials with longer durations, larger groups, and a more standardized methodological approach to investigate the safety and efficacy of pharmacological treatment in TS. A double-blind design should also be chosen, although in the case of significant treatment effects there is the risk that participants can work out which condition they have been assigned to. Finally, the negative effects of excessively high dropout rates for different causes should be considered with caution. In summary, treatment studies in TS require more effort than those for some other disorders.

As mentioned before and in other chapters, although TS is not a rare disease, only a minority of affected persons require pharmacological treatment. This creates obstacles to the development of new studies, given the lack of incentives (Fischer et al., 2005) and the limited interest on the part of the pharmaceutical industry. TS clinicians and researchers should be encouraged and, when possible, supported by TS patient associations (see Chapter 30) to develop, in the best-case scenario, worldwide consensus standards for all TS-specific methodological aspects of treatment studies (e.g., study duration, measurement of treatment and side effects, definition of refractoriness, etc.). Thereafter, lobbying for funding larger multicenter studies should be coordinated (e.g., in the United States and/or in Europe). Those studies should include the comparison of different agents and allow subgroup analyses of sufficiently homogenous groups in terms of age, comorbidity, etc.

In Box 24.2 we present outlooks for further studies on treatment agents, based on recent etiological and pathophysiological findings in TS. At first, the "old story" of TS as a "hyperdopaminergic illness" should be evaluated in more detail in view of recent work providing new evidence of the role of dopamine in TS, as well as its interactions with other neurotransmitters (e.g., glutamate, serotonin, and histamine). For example, in animal studies (see Chapter 15), systemic delivery of dopamine agonists and antagonists has identified differential stereotypical behavioral profiles depending on whether D1 receptors are stimulated through direct D1 specific agonists or upregulated through chronic exposure to specific D1 antagonists (Taylor et al., 2010). On the other hand, the idea underlying the use of dopamine agonists has been questioned in view of the news coming from the pharmaceutical company Boehringer Ingelheim, which arrested the clinical development of pramipexole, a D2/D3/D4 receptor agonist in pediatric TS, because there was no trend of improvement on pramipexole versus placebo in a 6-week, double-blind, randomized, placebo-controlled, flexible-dose

Table 24-2. Most Common and Important Medications for Treatment of TS and Other Chronic Tic Disorders

Medication	Indication	Start dosage (mg)	Therapeutic range (mg)	Frequent side effects	Physical examinations— at start and at control	Level of evidence
Alpha-Adrenergic Agonists						
Clonidine	ADHD/TS	0.05	0.1–0.3	Orthostatic hypotension, sedation, sleepiness	Blood pressure, ECG	A
Guanfacine	ADHD/TS	0.5–1.0	1.0–4.0	Orthostatic hypotension, sedation, sleepiness	Blood pressure, ECG	A
Typical Neuroleptics						
Haloperidol	TS	0.25–0.5	0.25–15.0	EPS, sedation, increased appetite	Blood count, ECG, weight, transaminases, neurological status, prolactin	A
Pimozide	TS	0.5–1.0	1.0–6.0	EPS, sedation, increased appetite	Blood count, ECG, weight, transaminases, neurological status, prolactin	A
Atypical Neuroleptics						
Aripiprazole	TS	2.50	2.5–30	Sedation, akathisia, EPS, headache, increased appetite (less than other neuroleptics), orthostatic hypotension	Blood count, blood pressure, weight, ECG, transaminases, blood sugar	C
Olanzapine	TS/OCB	2.5–5.0	2.5–20.0	Sedation, increased appetite, akathisia	Blood count, blood pressure, ECG, weight, electrolytes, transaminases, prolactin, blood lipids and sugar	B

(Continued)

Table 24-2. (Continued)

Medication	Indication	Start dosage (mg)	Therapeutic range (mg)	Frequent side effects	Physical examinations— at start and at control	Level of evidence
Quetiapine	TS	100–150	100–600	Sedation, increased appetite, agitation, orthostatic hypotension	Blood count, blood pressure, ECG, weight, electrolytes, transaminases, prolactin, blood lipids and sugar	C
Risperidone	TS/DBD	0.25	0.25–6.0	EPS, sedation, increased appetite, orthostatic hypotension	Blood count, blood pressure, ECG, weight, electrolytes, transaminases, prolactin, blood lipids and sugar	A
Ziprasidone	TS	5.0–10.0	5.0–30.0	EPS, sedation	Blood count, ECG, weight, transaminases, prolactin	A
Benzamides						
Sulpiride	TS/OCB	50–100 (2 mg/kg)	2–10 mg/kg	Problems with sleep, agitation, increased appetite	Blood count, ECG, weight, transaminases, prolactin, electrolytes	B
Tiapride	TS	50–100 (2 mg/kg)	2–10 mg/kg	Sedation, increased appetite	Blood count, ECG, weight, transaminases, prolactin, electrolytes	B

Listed in alphabetical order.
DBD, disruptive behavior disorder; OCB, obsessive-compulsive behavior; EPS, extrapyramidal symptoms. Evidence level: A (>2 RCTs), B (1 RCT), C (case studies, open trials).

Box 24.1.Key Points

- Because of the waxing and waning nature of tics, a meaningful appraisal of treatment efficacy in TS can be made in most cases only after a longer observation time.
- Environmental or situational factors have a modulating influence on tics, possibly biasing the appraisal of treatment efficacy.
- Many affected children, adolescents, and adults do not seek or require pharmacological treatment (tic severity: mild to moderate).
- Nonpharmacological and/or pharmacological interventions make sense for persons with subjective discomfort, social and/or emotional problems, functional interference, etc.
- The clinical experience is that pharmacotherapy induces faster and probably more prominent tic reduction than behavioral treatment options.
- The goal of pharmacological treatment is a reduction in tic symptoms.
- Antipsychotic drugs may lead to the most reliable and fastest treatment effectiveness, but they also pose the greatest risk of side effects.
- Risperidone can be considered a first-choice agent for the treatment of tics.
- Pimozide, tiapride, sulpiride, and aripiprazole are regarded as second-choice agents.
- Clonidine might be helpful mainly in patients with comorbid TS and ADHD.
- To provide high-quality evidence on pharmacological treatment in TS, future studies should include, for instance, longer observation periods, larger groups, more standardized methodological approaches, placebo controls, a double-blind design, etc.

study including a total of 63 patients aged 6 to 17 years with TS (43 on pramipexole, 20 on placebo; 58 of the 63 completed the trial) (http://trials.boehringer-ingelheim.com/res/trial/data/pdf/248.642_Statement.pdf). Secondly, two recent genetic studies (Ercan-Sencicek et al., 2010; Fernandez et al., 2012) reported evidence that diminished histaminergic neurotransmission might be associated with TS, at least in some patients. Accordingly, the authors suggested that raising brain histamine levels may decrease tics. To our knowledge, to date there is only one case report (Hartmann et al., 2011) of pharmacological treatment to modulate histaminergic neurotransmission in TS, describing a patient with comorbid narcolepsy without cataplexy, characterized by excessive daytime sleepiness and sleep disturbance; he received pitolisant, an inverse H3 receptor agonist that potentiates histaminergic neurotransmission. Previous trials of typical antipsychotics slightly decreased tics but induced fatigue and sedation, whereas stimulants exacerbated his tics dramatically. Treatment with pitolisant alleviated the narcolepsy with a positive effect also on his tics. Therefore, the authors concluded that, apart from tics, pitolisant may be helpful in treating attention deficit in children with TS and in reversing antipsychotic-induced daytime sleepiness. There are several hints of a close interrelationship between histaminergic and dopaminergic neurotransmission, particularly in the striatum (Ferrada et al., 2008). Controlled clinical trials of agents modulating histaminergic neurotransmission in TS patients are under way.

> A 9-year-old boy reported, over a period of approximately 2 years, a waxing and waning itching sensation, relieved by throat clearing and eye blinking. Additionally, he would stare at the ceiling lamp because this made his eyes feel better. Later on, facial grimacing, neck jerking, throat clearing, and high-pitched squeaking appeared, and he was referred to a TS

Box 24.2. Questions for Future Research

1. Does a specific drug really work in TS? Because of the limited evidence base and due to several difficulties in terms of the design of pharmacological trials in TS, more studies in larger and more homogeneous groups of affected persons with longer observation periods are urgently required.
2. How fast is the onset of effect of pharmacological versus behavioral treatment? What are the differences in their impact on the individual TS course? In daily clinical practice it seems likely that medication is associated with a faster onset of tic reduction but behavioral treatment might have a more "stable effect" (i.e., tic reduction remains after cessation of habit reversal).
3. What could be a definition of refractoriness of pharmacological treatment? Is there any evidence for polypharmacy? There is no evidence from clinical studies about polypharmacy, although it is often required in severe cases, particularly in the case of comorbid conditions such as ADHD, OCD, or depression or refractoriness to monotherapy.
4. Will medication reduce tics and/or premonitory urges? It is unclear if medication reduces tic severity and/or the premonitory urge. Maybe there are differences between the substances despite the same effect on tic amelioration.
5. How is stress modulated by anti-tic medication? Although there are several hints that stress has an impact on tic severity, there are no data about changes in stress by pharmacological treatment of tics.
6. What are the differences in efficacy and efficiency between pharmacological versus behavioral treatment (versus deep brain stimulation)? The evidence base (e.g., by comparing the effect sizes of single studies) concerning the efficacy and efficiency of pharmacological versus behavioral treatment or of their combination is very limited. Therefore, direct comparisons in one study (e.g., for ADHD) are urgently required.
7. Is it possible to develop individualized treatment plans based on genetic information? New and exciting genetic findings might open the possibility of starting the optimal individualized pharmacological treatment after genetic tests.

clinic. All symptoms could be controlled by volition, and there were no relevant problems during school hours. However, at home he reported a massive increase of symptom severity and subjective discomfort. Antihistaminic eyedrops and topical steroid nasal sprays had no positive effects. Prick testing to routine aeroallergens was negative. After TS was diagnosed, tiapride was initiated and after 8 weeks his tics had decreased dramatically.

Thirdly, and not only in the context of the poststreptococcal hypothesis (see Chapter 9), immunological abnormalities (Landau et al., 2012; Murphy et al., 2010) reported in TS patients (see Chapter 14) raise the question of whether antibiotic prophylaxis or immunomodulatory interventions can be helpful, at least in some susceptible TS patients (Hoekstra et al., 2004; Zykov et al., 2009). This question will remain unanswered until a clearer picture of the involvement of immunity in TS is provided by larger clinical studies that are under way (see www.emtics.eu).

Fourth, pharmacological modulation of GABAergic (inhibitory) and glutamatergic (excitatory) (Singer et al., 2010) neurotransmission in TS should be investigated in more detail. Finally, studies investigating the relationship of oxidative stress and TS are increasing, but therapeutic research is only just beginning (http://clinicaltrials.gov/show/NCT01172288).

REFERENCES

Anca MH, Giladi N, Korczyn AD. Ropinirole in Gilles de la Tourette syndrome. *Neurology* 2004; *62*:1626–1627.

Banaschewski TB, Neale BM, Rothenberger A, Roessner V. Comorbidity of tic disorders & ADHD: conceptual and methodological considerations. *Eur Child Adolesc Psychiatry* 2007; *16* Suppl 1:5–14.

Bestha DP, Jeevarakshagan S, Madaan V. Management of tics and Tourette's disorder: an update. *Expert Opin Pharmacother* 2010; *11*:1813–1822.

Bloch M, State M, Pittenger C. Recent advances in Tourette syndrome. *Curr Opin Neurol* 2011; *24*:119–125.

An excellent review of the whole TS field.

Borison RL, Ang L, Hamilton WJ, et al. Treatment approaches in Gilles de la Tourette syndrome. *Brain Res Bull* 1983; *11*:205–208.

Bressan RA, Jones HM, Pilowsky LS. Atypical antipsychotic drugs and tardive dyskinesia: relevance of D2 receptor affinity. *J Psychopharmacol* 2004; *18*:124–127.

Bruggeman RC, van der Linden RC, Buitelaar JK, et al. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry* 2001; *62*:50–56.

Cummings DD, Singer HS, Krieger M, et al. Neuropsychiatric effects of guanfacine in children with mild tourette syndrome: a pilot study. *Clin Neuropharmacol* 2002; *25*: 325–332.

Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's syndrome. *Cochrane Database Syst Rev* 2009:CD006565.

Debes N, Hjalgrim H, Skov L. The presence of attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder worsen psychosocial and educational problems in Tourette syndrome. *J Child Neurol* 2010; *25*:171–181.

Dion Y, Annable L, Sandor P, Chouinard G. Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2002; *22*:31–39.

Dose M, Lange HW. The benzamide tiapride: treatment of extrapyramidal motor and other clinical syndromes. *Pharmacopsychiatry* 2000; *33*:19–27.

Drtílková I. Clonazepam, clonidine and tiapride in children with tic disorder. *Homeostasis* 1996; *37*:216.

Du JC, Chiu TF, Lee KM, et al. Tourette syndrome in children: an updated review. *Pediatr Neonatol* 2010; *51*:255–264.

Du YS, Li HF, Vance A, et al. Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Aust N Z J Psychiatry* 2008; *42*:807–813.

The only trial comparing directly two agents for treatment of TS with a large sample size (n = 437).

Eddy CM, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. *Ther Adv Neurol Disord* 2011; *4*:25–45.

Eggers C, Rothenberger A, Berghaus U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. *Eur Arch Psychiatry Neurol Sci* 1998; *237*:223–229.

Ercan-Sencicek AG, Stillman AA, Ghosh AK, et al. L-histidine decarboxylase and Tourette's syndrome. *N Engl J Med* 2010; *362*: 1901–1908.

Fernandez TV, Sanders SJ, Yurkiewick IR, et al. Rare copy number variants in Tourette syndrome disrupt genes in histaminergic pathways and overlap with autism. *Biol Psychiatry* 2012; *71*:392–402.

Ferrada C, Ferré S, Casadó V, et al. Interactions between histamine H3 and dopamine D2 receptors and the implications for striatal function. *Neuropharmacology* 2008; *55*: 190–197.

Fischer A, Borensztein P, Roussel C. The European rare diseases therapeutic initiative. *PLoS Med* 2005; *2*:e243.

Fusco C, Bertani G, Caricati G, Della Giustina E. Stress fracture of the peroneal bone secondary to a complex tic. *Brain Dev* 2006; *28*:52–54.

Gaffney GR, Perry PJ, Lund BC, et al. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 2002; *41*:330–336.

George MS, Trimble MR, Robertson MM. Fluvoxamine and sulpiride in comorbid obsessive-compulsive disorder and Gilles de la Tourette syndrome. *Hum Psychopharmacol* 1993; *8*:327–334.

Gilbert DL, Batterson JR, Sethuraman G, Sallee FR. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *J Am Acad Child Adolesc Psychiatry* 2004; *43*:206–214.

Gilbert DL, Dure L, Sethuraman G, et al. Tic reduction with pergolide in a randomized controlled trial in children. *Neurology* 2003; *60*: 606–611.

Goetz CG. Clonidine and clonazepam in Tourette syndrome. *Adv Neurol* 1992; *58*:245–251.

Goetz CG, Stebbins GT, Thelen JA. Talipexole and adult Gilles de la Tourette's syndrome: double-blind, placebo-controlled clinical trial. *Mov Disord* 1994; *9*:315–317.

Hartmann A, Worbe Y, Arnulf I. Increasing histamine neurotransmission in Gilles de la Tourette syndrome. *J Neurol* 2011; *259*:375–376.

Hoekstra PJ, Minderaa RB, Kallenberg CG. Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry* 2004; *65*:537–542.

Interesting paper because of the publication of negative findings concerning the possible therapeutic value of findings based on the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) hypothesis.

Howson AL, Batth S, Ilivitsky V, et al. Clinical and attentional effects of acute nicotine treatment in Tourette's syndrome. *Eur Psychiatry* 2004; *19*:102–112.

Jankovic J, Jimenez-Shahed J, Brown L. A randomized, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. *J Neurol Neurosurg Psychiatry* 2010; *81*:70–73.

Jankovic J, Kurlan R. Tourette syndrome: Evolving concepts. *Mov Disord* 2011; *26*: 1149–1156.

Another interesting review of TS from a U.S. perspective; the selection of the presented findings on pharmacological treatment is subjective.

Kimber TE. An update on Tourette syndrome. *Curr Neurol Neurosci Rep* 2010; *10*:286–291.

Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. *Mov Disord* 1996; *11*:563–566.

Kurlan R. Clinical practice. Tourette's Syndrome. *N Engl J Med* 2010; *363*:2332–2338.

Kurlan R, McDermott MP, Deeley C, et al. Prevalence of tics in schoolchildren and association with placement in special education. *Neurology* 2001; *57*:1383–1388.

Landau YE, Steinberg T, Richmand B, et al. Involvement of immunologic and biochemical mechanisms in the pathogenesis of Tourette's syndrome. *J Neural Transm* 2012; *119*: 621–626.

Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989; *28*:566–573.

Lipinski JF, Sallee FR, Jackson C, Sethuraman G. Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide. *Mov Disord* 1997; *12*:402–407.

Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; *56*:605–610.

Meisel A, Winter C, Zschenderlein R, Arnold G. Tourette syndrome: efficient treatment with ziprasidone and normalization of body weight in a patient with excessive weight gain under tiapride. *Mov Disord* 2004; *19*:991–992.

Muller-Vahl KR, Krueger D. Does Tourette syndrome prevent tardive dyskinesia? *Mov Disord* 2011; *26*:2442–2443.

Muller-Vahl KR, Roessner V. Treatment of tics in patients with Tourette syndrome: Recommendations according to the European Society for the Study of Tourette Syndrome. *Mov Disord* 2011; *26*:2447.

Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; *35*:57–61.

The first trial on THC for treatment of TS. More studies are required.

Muller-Vahl KR, Schneider U, Prevedel H, et al. Delta-9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; *64*:459–465.

Muroni A, Paba S, Puligheddu M, et al. A preliminary study of finasteride in Tourette syndrome. *Mov Disord* 2011; *26*:2146–2147.

Murphy TK, Kurlan R, Leckman JF. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, and related disorders: a way forward. *J Child Adolesc Psychopharmacol* 2010; *20*:317–331.

Onofrj M, Paci C, D'Andreamatteo G, Toma L. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. *J Neurol* 2000; *247*:443–446.

Parraga HC, Harris KM, Parraga KL, et al. An overview of the treatment of Tourette's disorder and tics. *J Child Adolesc Psychopharmacol* 2010; *20*:249–262.

Peterson BS, Zhang H, Anderson GM, Leckman JF. A double-blind, placebo-controlled, crossover trial of an antiandrogen in the treatment of Tourette's syndrome. *J Clin Psychopharmacol* 1998; *18*:324–331.

Pierce A, Rickards HE. Atypical antipsychotics for Tourette's syndrome. *Cochrane Database Syst Rev* (in press).

Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. *Cochrane Database Syst Rev* 2009:CD006996.

Rickards H. Tourette's syndrome and other tic disorders. *Pract Neurol* 2010; *10*:252–259.

Riley DE, Lang AE. Pain in Gilles de la Tourette syndrome and related tic disorders. *Can J Neurol Sci* 1989; *16*:439–441.

Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000; *123*:425–462.

Robertson MM, Stern JS. Gilles de la Tourette syndrome: symptomatic treatment based on evidence. *Eur Child Adolesc Psychiatry* 2000; *9* Suppl 1:I60–75.

Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. *Eur Child Adolesc Psychiatry* 2011a; *20*:173–196.

The first consensus-based international guidelines on pharmacologcial treatment of TS; it presents a comprehensive overview of all studies on pharmacological treatment of TS.

Roessner V, Rothenberger A, Rickards H, Hoekstra PJ. European clinical guidelines for Tourette syndrome and other tic disorders. *Eur Child Adolesc Psychiatry* 2011b; *20*:153–154.

Ross MS, Moldofsky H. A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. *Am J Psychiatry* 1978; *135*:585–587.

The first randomized, double-blind, placebo-controlled trial comparing directly two agents for treatment of TS.

Rothenberger A, Banaschewski T, Roessner V. *Tic-Störungen. Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter. P. u. P. Deutsche Gesellschaft für Kinder- u. Jugendpsychiatrie*. Köln: Deutscher Ärzteverlag, 2007, pp. 319–325.

Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; *39*:292–299.

Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; *154*:1057–1062.

Sandor P. Pharmacological management of tics in patients with TS. *J Psychosom Res* 2003; *55*:41–48.

Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry* 2001; *158*:1067–1074.

Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003; *60*:1130–1135.

Shapiro AK, Shapiro ES, Young JG, Feinberg TE. Measurement in tic disorders. In Shapiro AK, Shapiro ES, Young JG, Feinberg TE. *Gilles de la Tourette syndrome*. New York: Raven Press, 1988, pp. 127–193.

Shapiro E, Shapiro AK, Fulop G, et al. Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; *46*:722–730.

One of the rare trials comparing directly two agents for treatment of TS of larger sample size.

Shapiro E, Shapiro E. Treatment of tic disorders with haloperidol. In Cohen DJ, Bruun RD, Leckman JF (Eds.), *Tourette syndrome and tic disorders*. New York: John Wiley and Sons, 1998, pp. 267–280.

Singer HS. Treatment of tics and Tourette syndrome. *Curr Treat Options Neurol* 2010; *12*:539–561.

Another interesting review of TS from a U.S. perspective; the selection of the presented findings on pharmacological treatment is subjective.

Singer HS, Morris C, Grados M. Glutamatergic modulatory therapy for Tourette syndrome. *Med Hypotheses* 2010; 74:862–867.

Interesting hypotheses for further research on pharmacological treatment of TS.

Singer HS, Wendlandt J, Krieger M, Giuliano J. Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. *Neurology* 2001; 56:599–604.

Smith-Hicks CL, Bridges DD, Paynter NP, Singer HS. A double-blind randomized placebo control trial of levetiracetam in Tourette syndrome. *Mov Disord* 2007; 22:1764–1770.

Taylor JL, Rajbhandari AK, Berridge KC, Aldridge JW. Dopamine receptor modulation of repetitive grooming actions in the rat: potential relevance for Tourette syndrome. *Brain Res* 2010; 1322:92–101.

Weisman H, Qureshi IA, Leckman JF, et al. Meta-analysis: Alpha-2 agonists in the treatment of tic disorders: moderating effects of ADHD. *Neurosci Biobehav Rev* 2012; Oct 23. [Epub ahead of print].

An important meta-analysis revolutionizing the evaluation of clonidine in the pharmacological treatment of tics.

Wenzel C, Kleimann A, Bokemeyer S, Muller-Vahl KR. Aripiprazole for the treatment of Tourette syndrome: a case series of 100 patients. *J Clin Psychopharmacol* 2012; 32:548–550.

Zykov VP, Shcherbina AY, Novikova EB, Shvabrina TV. Neuroimmune aspects of the pathogenesis of Tourette's syndrome and experience in the use of immunoglobulins in children. *Neurosci Behav Physiol* 2009; 39:635–638.

section F.2

OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Articles

Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years

Maria G. Motlagh[1*], Megan E. Smith[1], Angeli Landeros-Weisenberger[1], Andrew J. Kobets[2], Robert A. King[1], Joan Miravite[3], Alain C. J. de Lotbinière[4], Ron L. Alterman[5], Alon Y. Mogilner[6], Michael H. Pourfar[6], Michael S. Okun[7] & James F. Leckman[1]

[1] Child Study Center, Yale University, New Haven, Connecticut, United States of America, [2] Department of Neurosurgery, Montefiore Medical Center, Bronx, New York, United States of America, [3] Department of Neurology, Beth Israel, New York, New York, United States of America, [4] Department of Neurosurgery, New York College of Medicine, Valhalla, New York, United States of America, [5] Division of Neurosurgery, Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts, United States of America, [6] Departments of Neurosurgery and Neurology, New York University, Langone Medical Center, New York, New York, United States of America, [7] Departments of Neurology and Neurosurgery, Center for Movement Disorders & Neurorestoration, University of Florida, Gainesville, Florida, United States of America

Abstract

Background: Deep brain stimulation (DBS) remains an experimental but promising treatment for patients with severe refractory Gilles de la Tourette syndrome (TS). Controversial issues include the selection of patients (age and clinical presentation), the choice of brain targets to obtain optimal patient-specific outcomes, and the risk of surgery- and stimulation-related serious adverse events.

Methods: This report describes our open-label experience with eight patients with severe refractory malignant TS treated with DBS. The electrodes were placed in the midline thalamic nuclei or globus pallidus, pars internus, or both. Tics were clinically assessed in all patients pre- and postoperatively using the Modified Rush Video Protocol and the Yale Global Tic Severity Scale (YGTSS).

Results: Although three patients had marked postoperative improvement in their tics (>50% improvement on the YGTSS), the majority did not reach this level of clinical improvement. Two patients had to have their DBS leads removed (one because of postoperative infection and another because of lack of benefit).

Discussion: Our clinical experience supports the urgent need for more data and refinements in interventions and outcome measurements for severe, malignant, and medication-refractory TS. Because TS is not an etiologically homogenous clinical entity, the inclusion criteria for DBS patients and the choice of brain targets will require more refinement.

Keywords: Gilles de la Tourette syndrome, deep brain stimulation, globus pallidus internus, midline thalamic nuclei

Citation: Motlagh MG, Smith ME, Landeros-Weisenberger A, et al. Lessons learned from open-label deep brain stimulation for Tourette syndrome: eight cases over 7 years. *Tremor Other Hyperkinet Mov* 2013; 3: http://tremorjournal.org/article/view/170

*To whom correspondence should be addressed. E-mail: maria.motlagh@yale.edu

Editor: Elan D. Louis, Columbia University, United States of America

Received: April 12, 2013 **Accepted:** August 23, 2013 **Published:** November 1, 2013

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Introduction

Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by multiple motor and vocal tics lasting a minimum of 1 year. Tic disorders are frequently chronic, if not lifelong conditions. Usual clinical practice focuses initially on educational and supportive interventions. In addition, a recent multisite randomized clinical trial demonstrated the efficacy of comprehensive behavioral intervention for tics in a subset of pediatric and adult patients.[1,2] Nevertheless, most controlled treatments have focused on pharmacologic interventions. Although valuable in the management of individuals with TS, pharmacotherapy rarely eradicates tics completely, and many individuals have residual and clinically impairing symptoms.[3,4] Furthermore, some of the most effective medications for reducing tics can be associated with a range of adverse effects, and there is a small subset of patients who will not respond to either behavioral or pharmacologic approaches.[3]

Deep brain stimulation (DBS) has been introduced as an investigational approach for addressing some of the intractable symptoms of malignant TS. The stimulation targets that have been used in TS include: 1) the midline thalamic nuclei, with electrodes positioned at various points along the anterior–posterior axis (centromedian nucleus, parafascicular nucleus, and nucleus ventro-oralis internus); 2) the globus pallidus pars internus (GPi), either in the posteroventrolateral (somatosensory) region or the anteromedial (limbic) region; 3) the globus pallidus pars externus; 4) the nucleus accumbens/anterior limb of the internal capsule; and 5) the subthalamic nucleus (Table 1).[5–42]

While many of the TS patients reported in the literature have had beneficial short-term outcomes following DBS, randomized controlled studies of larger cohorts have not been performed. Although some surgeries are free of complications, a number of surgery-related serious adverse events (e.g. bleeding, infection, hardware malfunction) have been reported, as well as stimulation-related serious adverse events (e.g. nausea, eye movement abnormalities, sedation, anxiety, altered mood, changes in sexual function).[5–42] In general, the degree of tic improvement appears to be more robust for the thalamic and GPi targets. However, there is at least one case in which targeting the nucleus accumbens resulted in a marked improvement in self-injurious tics.[19]

This paper details the outcomes of eight additional patients with intractable, treatment-refractory TS who were treated with DBS. These patients had their DBS electrodes inserted at various times during a 7-year period (2004–2011), employing various targets and approaches based on the available knowledge at the time of implantation. Two distinct GPi sites (somatosensory [posteroventral] vs. limbic [anteromesial]) and midline thalamic sites were targeted. The initial outcome of the first patient discussed here has been previously reported.[12]

Methods

Patient selection

Each of the patients presented had severe malignant tics that impaired their quality of life and activities of daily living. Five of the patients exhibited self-injurious tics that either resulted in or threatened permanent neurologic injury. The decision to treat was taken on a case-by-case basis based on clinical necessity. Although we did not have *a priori* inclusion and exclusion criteria, all patients were required to have exhausted at least three known treatment options, including adequate trials with both a typical and atypical neuroleptic. The treatments had to be administered in adequate dosages and for at least 6 months.[43] Candidates could not have medical, neurologic, or psychiatric conditions that may have increased the risk of the procedure, precluded full participation (during the procedure or follow-up), or compromised the accuracy of the outcome assessment measures.[43,44] Four of the patients were ≥25 years of age at the time of the surgery and in only three patients was there a documented failed treatment trial with an α-adrenergic agonist. The decision to not require a failed trial with an α-adrenergic agonist was based on a clinical judgment that the length of time needed to complete an adequate trial (≥12 weeks) placed the individual at undue risk of permanent injury, and also the consideration that the degree of improvement, even if the trial was successful, would not be sufficient to reduce the risk of self-injury. Patient inclusion was based on the consensus of clinicians and the patient that the symptoms and their associated impairment were severe enough to justify surgery as a medical necessity.

Prior to surgery, the patients were evaluated by the team at Yale (M.G.M., R.A.K, A.L.-W.) as well as by the surgeons and other knowledgeable professionals (A.C.J.L. at Yale and New York College of Medicine; R.L.A. at Mt. Sinai and Beth Israel Deaconess Medical Center; and A.Y.M. and M.H.P. at North Shore-Long Island Jewish Health System). Comorbid conditions and other psychopathology and psychosocial factors were also assessed. Efforts were made to address any psychosocial issues that could affect patient participation and assessment prior to the surgical intervention, but no formal protocol was followed.

Surgical technique

Frame-based stereotactic targeting employing MRI (Magnetic Resonance Imaging) with or without CT (Computed Tomography) was used in each case. The stereotactic coordinates for the targeted anatomic structure were based on the best available data.[45–50] Typically, the initial coordinates, derived relative to the intercommissural plane, were then adjusted by direct visualization on the MRI, with or without the assistance of digital overlays of the *Schaltenbrand and Wahren Atlas*. Implantation trajectories were planned to avoid sulci and cortical vessels.

Intraoperative macrostimulation was performed to assess for adverse events with the exception of one patient (subject 7), who was consciously sedated throughout his second and third surgeries. During test stimulation the patients were asked to report any unwanted side effects, including but not limited to muscle spasms, persistent spontaneous sensations, pain, dizziness, and double vision. The implanted electrodes were secured to the skull employing accepted techniques and were connected to implantable pulse generators on the same day or shortly thereafter.

Postoperative management

Postoperative adjustments were performed by a DBS-trained clinician. The first session occurred 10–14 days following electrode implantation. A range of pulse widths (60–210 microseconds), stimulation rates (60–200 Hz), and electrode combinations were tested. Both monopolar and bipolar arrays were programmed empirically with the goal of achieving the greatest possible tic reduction with minimal side effects. Stimulation amplitudes varied from 0.1 to 5 V. Programming sessions were performed as needed, typically on a monthly basis for the first year and every 3–6 months thereafter. A summary of the active DBS contacts and lead locations is provided in Table 2.

Table 1. Published Studies on Deep Brain Stimulation in Tourette Syndrome

Target	Study	No. Patients	Follow-up, Months	Tic Improvement (YGTSS or MRVRS), %
Midline thalamus (CM–Pf/Voi, CM–Pf)	Visser-Vandewalle (2003)[5]	3	12, 8, 60	90, 72, 83
	Ackermans et al. (2006)[10] Ackermans et al. (2007)[11]	1 (CM–PF/Voi) 1 (CM–PF and postroventrolateral GPI)	12, 12	Tic 20 3 min, Tic 28 2 min
	Bajwa et al. (2007)[12]	1	24	66
	Maciunas et al. (2007)[14]	5	3	40 (Mean)
	Servello et al. (2008)[17]	18	3–18	65 (Mean)
	Shields et al. (2008)[20]	1	3	46
	Vernaleken et al. (2009)[21]	1	Not reported	36
	Porta et al. (2009)[25] Porta et al. (2012)[34]	15–18	24, 60–72 long-term follow-up (same cases)	52 (Mean) 41, 33, 32, 18, 1
	Servello et al. (2009)[26]	4	10–26	Slight to modest improvement
	Idris et al. (2010)[28]	1	2	Not reported
	Marceglia et al. (2010)[29]	7	6–24	33 (Mean)
	Ackermans et al. (2011)[30]	6	12	49 (Mean)
	Lee et al. (2011)[32]	1	18	58
	Kuhn et al. (2012)[35]	2	12	75 and 100
	Savica et al. (2012)[36]	3	12	70 (Mean)
	Maling et al. (2012)[37]	5	4–6	41, 33, 32, 18, 1
	Okun et al. (2013)[41]	5	6	19 (Mean)
GPi	Deidrerich et al. (2005)[6]	1	14	47–76
	Gallagher et al. (2006)[9]	1	Several	Disappearance of tics
	Ackermans et al. (2006)[10]	1 (CM–Pf and posteroventral GPi)	12	Tics 28 2/min
	Shahed et al. (2007)[15]	1	6	84
	Dehning et al. (2008)[16]	1	12	88
	Dueck et al. (2009)[22]	1	12	No improvement
	Martínez-Fernández et al. (2011)[31]	5 (one subject had both), 3 (posteroventral), 3 (anteromedial)	3–24	32, 19, 14, 63, 32, 19
	Cannon et al. (2012)[33]	11 (anteromedial)	4–30	51

Table 1. Continued

Target	Study	No. Patients	Follow-up, Months	Tic Improvement (YGTSS or MRVRS), %
	Dong et al. (2012)[39]	2 right GPi only (posteroventral)	12	59 and 53
	Massano et al. (2013)[42]	1 (anteromedial)	3, 12, 24	61
CM–Pf and/or GPi (anteromedial)	Houeto et al. (2005)[7]	1	24	82
	Welter et al. (2008)[18]	3	20, 27, 60	65–96
GPe	Piedimonte et al. (2013)[40]	1	3, 6, 24	39
A/C – NA	Flaherty et al. (2005)[8]	1	18	25
	Kuhn et al. (2007)[13]	1	30	41
	Zabek et al. (2008)[19]	1	28	80
	Neuner et al.(2009)[24]	1	36	44
	Burdick et al. (2010)[27]	1	39	15% worse
	Sachdev et al. (2012)[38]	1	8	57
STN	Martinez-Torres et al. (2009) [23]	1	12	76

Abbreviations: A/C, Anterior Limb of Internal Capsule; CM–Pf, Centromedial–Parafascicular Complex; GPe, Globus Pallidus, Pars Externus; GPi, Globus Pallidus, Pars Internus; MRVRS, Modified Rush Videotape Rating Scale; NA, Nucleus Accumbens; STN, Subthalamic Nucleus; Voi, Ventralis Oralis; YGTSS, Yale Global Tic Severity Scale.

Assessments

The *Diagnostic and Statistical Manual, 4th edition, Text Revised* (DSM-IV-TR) criteria for TS and comorbid diagnosis were used in this study to establish an official diagnosis.[51] We administered additional rating scales at baseline, including the Yale Global Tic Severity Scale (YGTSS),[52] the Yale–Brown Obsessive–Compulsive Scale,[53] the Hamilton Depression Rating Scale,[54] and the Hamilton Anxiety Rating Scale.[55] These assessments were also conducted at various intervals from 1 month to 6 years after surgery. Marked improvements were defined as more than 50% improvement in the Total Tic Score on the YGTSS (range 0–50). These evaluations were not performed in a scripted fashion as the DBS therapy was not provided as part of a prospective trial, but rather on a humanitarian basis.

Results

The clinical characteristics of the eight patients with TS at baseline are summarized in Table 3. As detailed in Table 3, three of the patients under the age of 25 years had severe malignant self-injurious tics. Baseline characteristics of tics and associated symptoms, together with follow-up evaluations for the eight subjects, are detailed in Table 4. We observed significant reduction in tic severity in three TS patients (subjects 1, 6 and 8; see Supplementary Materials). The range of improvement in the YGTSS Total Tic Score for the entire group was 0–85%. The mean percent improvement was 45%, and the median value was between 20% and 44%.

Two of eight subjects have had their electrodes removed. In one this was because of postoperative infection (subject 2), and in the other because of lack of therapeutic benefit after 3 years of stimulation (subject 3) (see Supplementary Materials for presentations of each case). At present, one individual has turned off his electrodes but continues to show a clear benefit (tic reduction) despite a gradual worsening of his overall neurologic status (subject 1, see below and Supplementary Materials).

Discussion

There are many unknowns when considering DBS for TS. These include the optimal target, the best indications for surgery, the optimal stimulation parameters, the optimal approach to assess social status, and the potential for social reintegration postsurgery.[41,43,44,56–58]

Patient selection

In this series, the two youngest patients (subjects 6 and 8) benefited the most from surgery and, thus far, these two patients have also been most successful in resuming a reasonably 'normal' life, with good to excellent reintegration into society. These individuals have also been successfully withdrawn from psychoactive medications, thus freeing them from potential side effects. The third individual (subject 1) who

Table 2. Stimulation Parameters and Lead Location at Follow-up Evaluation for all Subjects

Patient	Location	Identification of the Anatomic Target	DBS Settings
1 [a]	Thalamus	Leksell frame, MRI intraoperative guidance, general anesthesia (propofol), macrostimulation used, no microelectrode recording	*R 5-7+, 2.5 V, 210 μs, 185 Hz
	X (mm lateral AC-PC)=5		*L 1-3+, 2.35 V, 180 μs, 185 Hz
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
	GPi (posteroventral/sensorimotor)		*R 5-C+, 1.0 V, 120 μs, 130 Hz
	X (mm lateral to intercommissural)=17		*L 1-2+, 1.0 V, 120 ∀ μs, 130 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		
2 [b]	Thalamus	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	NA
	X (mm lateral AC-PC)=5		
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
3 [c]	Thalamus	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	NA
	X (mm lateral AC-PC)=5		
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
4	GPi (posteroventral/sensorimotor)	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	R 2-C+, 2. 5 V, 90 μs, 185 Hz
	X (mm lateral to intercommissural)=17		L 2-C+, 2.0 V, 90 μs, 185 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		
5	GPi (posteroventral/sensorimotor)	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	R 4+6-5-7+, 2.1 V, 180 μs, 185 Hz
	X (mm lateral to intercommissural)=17		L 2-1-0-C+, 2.1 V, 180 μs, 185 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		

Table 2. Continued

Patient	Location	Identification of the Anatomic Target	DBS Settings
6	Thalamus	Leksell frame, MRI/CT fusion, procedure performed under local anesthesia with dexmedetomidine used for sedation	R 1-C+, 3.0 V, 90 μs, 130 Hz
	X (mm lateral AC-PC) =5		L 1-C+, 3.2 V, 90 μs, 130 Hz
	Y (mm posterior AC-PC) = 4		
	Z (mm beneath AC-PC) = 0		
		Physiologic confirmation with microelectrode recording and macrostimulation	
7	GPi, anterior mesial (limbic)	Leksell frame, MRI intraoperative guidance, sedation with dexmedetomidine/propofol, physiologic confirmation with microelectrodes recording only	*R 1-C+, 3.0 V, 150 μs, 90 Hz
	X (mm lateral to intercommissural)=14		*L 1-C+, 2.5 V, 180 μs, 120 Hz
	Y (mm anterior to mid-commissural)=18		
	Z (mm deep to mid-commissural)=5		
	Thalamus		*R 11-C+, 2.0 V, 60 μs, 120 Hz
	X (mm lateral AC-PC)=6		*L 9-10-C+, 3.0 V, 60 μs, 120 Hz
	Y (mm posterior AC-PC)=3		
	Z (mm beneath AC-PC)=0		
	GPi (posteroventral/sensorimotor)		R 8-C+, 2.5 V, 90 μs, 185 Hz
	X (mm lateral to intercommissural)=17		*L 8-C+, 2.5 V, 90 μs, 180 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		
8	Thalamus	Leksell frame, MRI/CT fusion, procedure performed under general anesthesia with propofol and remifentanil	R C+1-, 2.1 V, 90 μs, 130 Hz
	X (mm lateral AC-PC)=5		L C+1-, 1.9 V, 90 μs, 130 Hz
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		

Table 2. Continued

Patient	Location	Identification of the Anatomic Target	DBS Settings
		Physiologic confirmation with microelectrode recording and macrostimulation	

Abbreviations: AC, Anterior Commissural; DBS, Deep Brain Stimulation; GPi, Globus Pallidus Pars Internus; PC, Posterior Commissural; NA: Not Applicable.
The DBS settings show right side (R), left side (L), voltage (V), pulse width (μs), and rate (Hz).
[a]GPi electrodes are not currently functional secondary to forceful head-snapping tics that led to electrode dysfunction.
[b]Electrodes were removed because of infection.
[c]Electrodes were removed because of lack of therapeutic benefit.
*Electrodes are currently turned OFF.

also had a 'marked improvement' remains disabled, despite being virtually tic free for significant periods of time. His disability is a consequence of permanent and progressive spinal injury secondary to an extremely forceful whole-body and head-snapping tic.[12] The forcefulness of this malignant tic has not been lessened by DBS, but its frequency has been markedly reduced despite the fact that his electrodes have been turned off for more than 8 months (see Supplementary Materials, subject 1). While these results may argue for earlier surgical intervention, it is also worth noting that subject 1 has more recently experienced a failure of his GPi leads because of wire fractures resulting from the forceful head snapping. These observations, albeit in a small number of patients, mirror the published experiences with DBS at the globus pallidus for primary generalized dystonia.[59,60] Here, too, younger patients and those who had not yet developed secondary skeletal changes responded more quickly and more robustly to DBS.

In typical TS, tics usually improve by 20 years of age, an observation that is often cited to support the view that surgery should not be considered prior to 25 years of age.[43,61] However, it is important to note that TS is a heterogeneous clinical entity and that the prevalence and severity of tics and the behavioral and emotional comorbidities observed in TS are both higher in younger patients.[62,63] In addition, tics and comorbidities in young people with severe refractory TS often have a strong association with difficulties encountered in remaining in school and maintaining normal peer relationships. It is also the case that younger patients are less likely to have sustained significant physical injury because of their tics. These observations suggest that surgical intervention prior to 25 years of age may be indicated in highly selected patients. Our current view is that a strict cut-off for eligibility based on age alone may exclude reasonable candidates, and that as in Parkinson's disease, age should be just one of many factors considered when determining an individual patient's surgical candidacy.

Target

In four patients, the tics virtually disappeared for 10–14 days immediately after surgery. In one patient (subject 1) the midline thalamic site was the target and in three patients (subjects 4, 5, and 7) the GPi (two sensorimotor and one limbic) was the target. This disappearance of tics might be attributable to the immediate trauma of the electrode placement (the so-called microlesion effect). Alternatively, it might represent a placebo response. Regardless of the underlying cause, in our experience this immediate response is *not* indicative of a long-term improvement in tic symptoms.

In the current case series, we report significant reductions in tic severity in three TS patients (subjects 1, 6, and 8) with electrode placement in the midline thalamic nuclei. Servello et al. reported a similar response to DBS (although to differing degrees) in 18 similarly treated patients with severe TS.[17] Subject 1 showed a further significant benefit with the placement of a second set of electrodes in the sensorimotor GPi. Indeed, this patient experienced periods during which he reported being virtually tic free for the first time in more than 40 years. The other patients had disappointing outcomes from their surgeries. However, a longer follow-up interval is needed in at least one patient (subject 7, who had DBS electrodes placed in both GPi sites as well as in the midline thalamic nuclei) before we can make this statement with certainty.

A 'definitive neuroanatomic target' for TS DBS has not yet emerged. The reasons for this are many. First, the specific neuronal circuitry underlying TS is only partially known.[64–71] In fact, it is not known if the pathophysiology of TS is the same for all patients, or if different types of TS patients have similar or dissimilar pathophysiologies requiring distinct neuromodulatory strategies. This is especially true for many of the patients in this series, given their severe, refractory tics, which often failed to show the typical bouts during the course of a day, or alternatively the waxing and waning course of weeks to months. Compounding these gaps in our knowledge is a lack of representative animal models for TS.[72] Finally, the best location for stimulation within each target (i.e. thalamus or GPi) may be very specific, and to date we are unable to refine the target physiologically as is the case for Parkinson's disease.[50,73]

A prevailing model of TS and other hyperkinetic movement disorders (including dystonia and chorea) implicates a low firing rate in output neurons of the GPi as a pathophysiologic hallmark.[74,75] However, recent observations suggest that the GPi activity seen in dystonia and tic disorders may be similar to that encountered in

Table 3. Baseline Clinical Characteristics of the Eight Patients with Tourette Syndrome

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
1	M	48	45	Eye blinking, violent head jerks, throwing elbow against ribs, abdominal tensing, snapping, grunting, screeching, coprolalia	No	Yes, slamming forearm against forehead	OCD (mild to moderate), depression	No	Separated, employed part time	Haloperidol, pimozide, risperidone, clonidine, fluoxetine, clonazepam, pergolide	Haloperidol, fluoxetine gabapentin, tizanidine, diazepam, temazepam, aspirin
2 [a]	M	44	41	Eye movements, facial tics, head jerking and snapping, shoulder shrugs, grunting, throat clearing	Yes	Yes, skin picking	OCD (severe)	Yes	Unmarried, self-employed	Pimozide, risperidone, olanzapine, quetiapine, fluoxetine, fluvoxamine, sertraline, clomipramine, clonazepam	Sertraline, clonazepam

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
3 [b]	M	37	27	Head and neck movements, body jerking, shifting body position, tongue movements, hand and arm tensing, bumping objects into teeth, toe curling, diaphragmatic dystonic tics limiting ability to breathe	No	No	OCD, attention-deficit disorder, anxiety symptoms	No	Unmarried, employed	Haloperidol, pimozide, clonidine, fluoxetine, sertraline, clonazepam	Clonidine, clonazepam,
4	M	42	38	Facial grimacing, flopping hands in front of face, pointing finger back and front, chest rubbing, grunting, yelling, whistling, curse words	No	No	OCD, history of ADHD	No	Unmarried, unemployed	Haloperidol, pimozide, clonazepam, methylphenidate	Clonazepam

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
5	M	24	15	Head jerks, snapping arm against side, kicking, licking items, head grabbing, copropraxia, loud screaming, sniffing	Yes	Yes, punching, hitting himself	OCD	Yes	Married, one child, unemployed	Haloperidol, pimozide, risperidone, fluphenazine, clonidine, fluvoxamine, imipramine, nortriptyline, clonazepam, pergolide	Clonazepam, quetiapine, zolpidem, topiramate, nicotine patches, ketamine, opiates
6	M	16	13	Eye blinking, head and shoulder jerking, head bobbing, flexion and extension of arms and fingers, spinning in place, throat clearing, coprolalia	Yes	No	ADHD	No	Unmarried, high-school student	Risperidone, aripiprazole, ziprasidone, sertraline, tetrabenazine, methylphenidate, topiramate	None

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
7	M	19	11	Dystonic posturing, exclusively left-sided tics and self-injurious behaviors such as poking left cornea and pulling on left eye lid, repeating single words or syllables	No	Yes poking left eye and pulling on left eye lid, left cheek biting	OCD, some symptoms of ADHD	No	Unmarried, unemployed	Haloperidol, risperidone, aripiprazole, fluphenazine, sertraline, clonazepam, tetrabenazine, guanfacine, topiramate, etanercept, N-acetyl cysteine	Haloperidol, clonazepam, clonidine, clonazepam, sertraline, carbamazepine

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
8	M	17	13	Atypical long bouts of severe tics (20 minutes to 1 hour) interspaced with long tic-free periods, tics include opening mouth wide, arm and shoulder movements, head and neck jerks, rapidly shaking head from side to side, gyrating head, arching back, flexion and extension of arms one side at a time	No	Yes, pounding of chest, punching forehead	OCD, mild depression, some symptoms of general anxiety disorder	Yes for OCD	Unmarried, student	Pimozide, risperidone, ziprasidone, aripiprazole, fluphenazine, clonidine, guanfacine, fluoxetine, clonazepam, topiramate	None

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; M, Male; OCD, Obsessive–Compulsive Disorder.

Positive family history: a first-degree (parent, sibling, child) or second-degree (grandparent, aunt, uncle, nephew, niece, half-sibling or a grandchild) relative with a chronic tic disorder. For additional clinical details, see Supplementary Materials.

[a]The electrodes removed due to side effect of infection.

[b]The electrodes removed due to a lack of therapeutic benefit.

Table 4. Individual Changes in Severity of Tics and Associated Behaviors in Eight Patients with Tourette Syndrome

Patients	Duration of Follow-up (Months)	YGTSS*		YBOCS***		HDRS		HARS	
		Before Surgery	At Last Follow-up**	Before Surgery	At Last Follow-up	Before Surgery	At Last Follow-up	Before Surgery	At Last Follow-up
1	107	36	10 (72%)	29	8	10	15	0	0
2[a]	95	41	32 (20%)	15	0	0	0	5	1
3[b]	84	43	40 (7%)	20	27	5	4	20	15
4	51	50	40 (20%)	12	10	3	3	4	3
5	8	38	22 (44%)	0	0	4	1	5	3
6	16	46	7 (85%)	5	5	0	0	2	1
7[c]	37	25	25 (0%)	0	0	3	15	3	3
8	6	43	14 (67%)	20	22	2	0	3	3

Abbreviations: HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; YBOCS, Yale–Brown Obsessive–Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

*Total tic severity does not include impairment score and is based on the worst-ever tic severity measured at the time of interview.

**Percent improvement in the YGTSS Total Tic Score.

***Obsessive–compulsive symptom severity is based on the total obsessive–compulsive severity measured at the time of interview.

[a]Electrodes were removed because of infection.

[b]Electrodes were removed because of lack of therapeutic benefit.

[c]This patient does not have any vocal tics.

Parkinson's disease[75–79] and, if true, this could challenge existing physiologic models. More data regarding TS physiology are needed before definitive conclusions can be drawn.

Because of the wide interpatient variability in specific tic symptoms and comorbidities, it still seems appropriate to consider multiple potential targets for DBS and to select targets based on the specific clinical characteristics of each patient. Another important factor that may complicate the interpretation of surgical results is that the amount of electrical energy delivered to a target can be very different from one patient to another, and even between hemispheres for the same patient. In some studies, the current intensity and spread have been so high that it is doubtful whether the effects of DBS are restricted to the specific target area.

Postoperative complications

In our case series, one patient (subject 2) developed an infection secondary to picking at the incision sites. Interestingly, in one recent study patients with TS were found to have a higher incidence of infectious complications following DBS than patients with Parkinson's disease or dystonia.[80] The basis of this increase is unknown, but conceivably could be related to host-specific immune factors as there is a growing body of evidence implicating immune dysregulation in TS patients.[81]

Programming

In addition to careful intraoperative targeting, thoughtful and labor-intensive programming of the stimulators is very important to achieving optimal clinical outcomes (see case material for subject 4). The potential need for frequent programming should be considered when choosing candidates for surgery, and families need to be fully apprised of this reality preoperatively. Although a monthly checkup for optimization and programming following DBS (for the first 6 months) is a reasonable standard in movement disorders, in our experience a more flexible schedule can be necessary for TS patients. Reasons for this include natural symptom fluctuations and variability in patients' responses to treatment and expectations. We had similar programming experiences to Porta et al.[25]

Confounding factors of the present report include multiple surgeons (three surgeons in five different centers) employing varied techniques, as well as the use of unblinded assessments. At the present time there is no consensus regarding the use of DBS in TS, although most experts believe it should be used as a last resort in a small subset of individuals who have severe, self-injurious tics or tics that are both refractory to treatment and severely impair quality of life. Randomized trials employing blinded ratings of patients treated by experienced DBS teams are sorely needed.[41] Finally, a deeper understanding of the circuitry involved in TS may lead to more successful tailored targeting for patients with refractory and malignant TS. Presently, however,

clinicians should be aware that outcomes are mixed and that 'one size does not fit all.'

Acknowledgment

The authors thank the study families and participants for taking part in this study. The authors also wish to thank Nancy Thompson for her invaluable assistance in completing this study.

References

1. Centini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA* 2010;303:1929–1937.

2. Helm S, Peterson AL, Piacentini J, et al. Randomized trial of behavior therapy for adults with Tourette syndrome. *Arch Gen Psychiatry* 2012;69:795–803.

3. Ger HS. Treatment of tics and Tourette syndrome. *Curr Treat Options Neurol* 2010;12:539–561.

4. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: pharmacological treatment of tic disorders—efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev* 2013;37:1162–1171.

5. Visser-Vandewalle V, Temel Y, Boon P, et al. Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. *J Neurosurg* 2003;99:1094–1100.

6. Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, Alesch F. Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: a case report. *Mov Disord* 2005;20:1496–1499.

7. Houeto JL, Karachi C, Mallet L, et al. Tourette's syndrome and deep brain stimulation. *J Neurol Neurosurg Psychiatry* 2005;76:992–995.

8. Flaherty AW, Williams ZM, Amirnovin R, et al. Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: technical case report. *Neurosurgery* 2005;57:E403.

9. Gallagher CL, Garell PC, Montgomery EB. Hemi tics and deep brain stimulation. *Neurology* 2006;66:E12.

10. Ackermans L, Temel Y, Cath D, et al. Deep brain stimulation in Tourette's syndrome: two targets? *Mov Disord* 2006;21:709–713.

11. Ackermans L, Temel Y, Bauer NJ, Visser-Vandewalle V; Dutch-Flemish Tourette Surgery Study Group. Vertical gaze palsy after thalamic stimulation for Tourette syndrome: case report. *Neurosurgery* 2007;61:E1100.

12. Bajwa RJ, de Lotbinière AJ, King RA, et al. Deep brain stimulation in Tourette's syndrome. *Mov Disord* 2007;22:1346–1350.

13. Kuhn J, Lenartz D, Mai JK, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. *J Neurol* 2007;254:963–965.

14. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *J Neurosurg* 2007;107:1004–1014.

15. Shahed J, Poysky J, Kenney C, Simpson R, Jankovic J. GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. *Neurology* 2007;68:159–160.

16. Dehning S, Mehrkens JH, Müller N, Bötzel K. Therapy-refractory Tourette syndrome: beneficial outcome with globus pallidus internus deep brain stimulation. *Mov Disord* 2008;23:1300–1302.

17. Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. *J Neurol Neurosurg Psychiatry* 2008;79:136–142.

18. Welter M, Mallet L, Houeto J, et al. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Arch Neurol* 2008;65:952–957.

19. Zabek M, Sobstyl M, Koziara H, Dzierzecki S. Deep brain stimulation of the right nucleus accumbens in a patient with Tourette syndrome. Case report. *Neurol Neurochir Pol* 2008;42:554–559.

20. Shields DC, Cheng ML, Flaherty AW, Gale JT, Eskandar EN. Microelectrode-guided deep brain stimulation for Tourette syndrome: within-subject comparison of different stimulation sites. *Stereotact Funct Neurosurg* 2008;86:87–91.

21. Vernaleken I, Kuhn J, Lenartz D, et al. Bithalamical deep brain stimulation in Tourette syndrome is associated with reduction in dopaminergic transmission. *Biol Psychiatry* 2009;66:e15–e17.

22. Dueck A, Wolters A, Wunsch K, et al. Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe Tourette syndrome and mental retardation. *Neuropediatrics* 2009;40:239–242.

23. Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, Limousin P. Improvement of tics after subthalamic nucleus deep brain stimulation. *Neurology* 2009;72:1787–1789.

24. Neuner I, Podoll K, Janouschek H, Michel TM, Sheldrick AJ, Schneider F. From psychosurgery to neuromodulation: deep brain stimulation for intractable Tourette syndrome. *World J Biol Psychiatry* 2009;10:366–376.

25. Porta M, Brambilla A, Cavanna AE, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. *Neurology* 2009;73:1375–1380.

26. Servello D, Sassi M, Brambilla A, et al. *De novo* and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: a multiple case report. *J Neurol* 2009;256:1533–1539.

27. Burdick A, Foote KD, Goodman W, et al. Lack of benefit of accumbens/capsular deep brain stimulation in a patient with both tics and obsessive-compulsive disorder. *Neurocase* 2010;16:321–330.

28. Idris Z, Ghani AR, Mar W, et al. Intracerebral haematomas after deep brain stimulation surgery in a patient with Tourette syndrome and low factor XIIIA activity. *J Clin Neurosci* 2010;17:1343–1344.

29. Marceglia S, Servello D, Foffani G, et al. Thalamic single-unit and local field potential activity in Tourette syndrome. *Mov Disord* 2010;25:300–308.

30. Ackermans L, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain* 2011;134: 832–844.

31. Martínez-Fernández R, Zrinzo L, Aviles-Olmos I, et al. Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus. *Mov Disord* 2011;10.1002.

32. Lee MW, Au-Yeung MM, Hung KN, Wong CK. Deep brain stimulation in a Chinese Tourette's syndrome patient. *Hong Kong Med J* 2011;17:147–150.

33. Cannon E, Silburn P, Coyne T, O'Maley K, Crawford JD, Sachdev PS. Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *Am J Psychiatry* 2012;169:860–866.

34. Porta M, Servello D, Zanaboni C, et al. Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. *Acta Neurochir (Wien)* 2012;154:2029–2041.

35. Kuhn J, Janouschek H, Raptis M, et al. *In vivo* evidence of deep brain stimulation-induced dopaminergic modulation in Tourette's syndrome. *Biol Psychiatry* 2012;71:e11–e13.

36. Savica R, Stead M, Mack KJ, Lee KH, Klassen BT. Deep brain stimulation in Tourette syndrome. *Mayo Clin Proc* 2012;87:59–62.

37. Maling N, Hashemiyoon R, Foote KD, Okun MS, Sanchez JC. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette's syndrome. *PLoS One* 2012;7:e44215.

38. Sachdev PS, Cannon E, Coyne TJ, Silburn P. Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette's syndrome. *BMJ Case Rep* 2012;2012.

39. Dong S, Zhuang P, Zhang XH, Li JY, Li YJ. Unilateral deep brain stimulation of the right globus pallidus internus in patients with Tourette's syndrome: two cases with outcomes after 1 year and a brief review of the literature. *J Int Med Res* 2012;40:2021–2028.

40. Piedimonte F, Andreani JC, Piedimonte L, et al. Behavioral and motor improvement after deep brain stimulation of the globus pallidus externus in a case of Tourette's syndrome. *Neuromodulation* 2013;16:55–58.

41. Okun MS, Foote KD, Wu SS, et al. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. *JAMA Neurol* 2013;70:85–94.

42. Massano J, Sousa C, Foltynie T, Zrinzo L, Hariz M, Vaz R. Successful pallidal deep brain stimulation in 15-year-old with Tourette syndrome: 2-year follow-up. *J Neurol* 2013;260:2417–9.

43. Mink JW, Walkup J, Frey KA, et al. Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Mov Disord* 2006;21:1831–1838.

44. Müller-Vahl KR, Cath DC, Cavanna AE, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: deep brain stimulation. *Eur Child Adolesc Psychiatry* 2011;20:209–217.

45. Lozano AM. Globus pallidus internus pallidotomy for generalized dystonia. *Mov Disord* 1997;12, 865–870.

46. Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. *Neurology* 1998: 51:1063.

47. Porta M, Sassi M, Ali F, Cavanna AE, Servello D. Neurosurgical treatment for Gilles de la Tourette syndrome: the Italian perspective. *J Psychosom Res* 2009;67:585–590.

48. Hariz MI, Robertson MM. Gilles de la Tourette syndrome and deep brain stimulation. *Eur J Neurosci* 2010;32:1128–1134.

49. Sassi M, Porta M, Servello D. Deep brain stimulation therapy for treatment-refractory Tourette's syndrome: a review. *Acta Neurochir (Wien)* 2011; 153:639–645.

50. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 2011;68:165.

51. American Psychiatric Association. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders, 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

52. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989;28:566–573.

53. Goodman WK, Price LH, Rasmussen SA, et al. (1989). The Yale-Brown Obsessive Compulsive Scale. *Arch Gen Psychiatry* 1989;46:1006–1011.

54. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278–296.

55. Hamilton M. The assessment of anxiety states by rating. *Brit JMed Psychology* 32:50–56.

56. Porta M, Sevello D, Sassi M, et al. Issues related to deep brain stimulation for treatment-refractory Tourette's syndrome. *Eur Neurol* 2009;62:264.

57. Porta M, Sassi M, Menghetti C, Servello D. The need for a proper definition of "treatment refractoriness" in Tourette syndrome. *Front Integr Neurosci* 2011;5:22.

58. Porta M, Sassi M, Servello D. Surgical treatment of Tourette syndrome. In: Martino D, Leckman JF (eds). Tourette syndrome. Oxford, UK: Oxford University Press; 2013; pp. 583–604.

59. Bressman S. Treatment of generalized dystonia. *Curr Treat Options Neurol* 2011;13:274–289.

60. Lubarr N, Bressman S. Treatment of generalized dystonia. *Curr Treat Options Neurol* 2011;13:274–289.

61. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med* 2006;160:65–69.

62. Chang HL, Liang HY, Wang HS, Li CS, Ko NC, Hsu YP. Behavioral and emotional problems in adolescents with Tourette syndrome. *Chang Gung Med J* 2008;31:145–152.

63. Leckman JF, Bloch MH, Scahill L, King RA. Tourette syndrome: the self under siege. *J Child Neurol* 2006;21:642–649.

64. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatr Neurol* 2001;25:190–198.

65. Bohlhalter S, Goldfine A, Matteson S, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain* 2006;129:2029–2037.

66. Lerner A, Bagic A, Boudreau EA, et al. Neuroimaging of neuronal circuits involved in tic generation in patients with Tourette syndrome. *Neurology* 2007;68:1979–1987.

67. Hampson M, Tokoglu F, King RA, Constable RT, Leckman JF. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. *Biol Psychiatry* 2009;65:594–599.

68. Church JA, Fair DA, Dosenbach NU, et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. *Brain* 2009;132:225–38.

69. Pourfar M, Feigin A, Tang CC, et al. Abnormal metabolic brain networks in Tourette syndrome. *Neurology* 2011;76:944–952.

70. Zebardast N, Crowley MJ, Bloch MH, Mayes LC, Leckman JF, Pelphrey KA, Swain. Brain mechanisms for prepulse inhibition in adults with Tourette syndrome: initial findings. *Psychiatry Res* 214:33–41.

71. Kataoka Y, Kalanithi PS, Grantz H, et al. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. *J Comp Neurol* 2010;518:277–291.

72. McCairn K, Imamura Y, Isoda M. Animal models of tics. In: Martino D, Leckman JF (eds). Tourette syndrome. Oxford, UK: Oxford University Press; 2013; pp. 329–358.

73. Jankovic J. Tourette's syndrome. *N Engl J Med* 2001;345:1184–1192.

74. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999;46:22–35.

75. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 1994;117:877.

76. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: implications for models of dystonia. *Ann Neurol* 2003;53:480–488.

77. Zhaung P, Li Y, Hallett M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia. *Clin Neurophysiol* 2004;115:2542–2557.

78. Zhuang P, Hallett M, Zhang X, Li J, Zhang Y, Li Y. Neuronal activity in the globus pallidus internus in patients with tics. *J Neurol Neurosurg Psychiatry* 2009;80:1075–1081.

79. Marceglia S, Servello D, Foffani G, et al. Thalamic single-unit and local field potential activity in Tourette syndrome. *Mov Disord* 2010;15:300–308.

80. Servello D, Sassi M, Gaeta M, Ricci C, Porta M. Tourette syndrome bears a higher rate of inflammatory complications at the implanted hardware in deep brain stimulation. *Acta Neurochir (Wien)* 2011;153:629–632.

81. Murphy TK, Kurlan R, Leckman J. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus*, and related disorders: a way forward. *J Child Adolesc Psychopharmacol* 2010;20:317–331.

Sections G & H

Behavioural Neurology 27 (2013) 119–124
DOI 10.3233/BEN-120276
IOS Press

Treatment of Tourette syndrome with cannabinoids

Kirsten R. Müller-Vahl
Clinic of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany
Tel.: +49 511 5323551; Fax: +49 511 5323187; E-mail: mueller-vahl.kirsten@mh-hannover.de

Abstract. Cannabinoids have been used for hundred of years for medical purposes. To day, the cannabinoid delta-9-tetrahydrocannabinol (THC) and the cannabis extract nabiximols are approved for the treatment of nausea, anorexia and spasticity, respectively. In Tourette syndrome (TS) several anecdotal reports provided evidence that marijuana might be effective not only in the suppression of tics, but also in the treatment of associated behavioural problems. At the present time there are only two controlled trials available investigating the effect of THC in the treatment of TS. Using both self and examiner rating scales, in both studies a significant tic reduction could be observed after treatment with THC compared to placebo, without causing significant adverse effects. Available data about the effect of THC on obsessive-compulsive symptoms are inconsistent. According to a recent Cochrane review on the efficacy of cannabinoids in TS, definite conclusions cannot be drawn, because longer trials including a larger number of patients are missing. Notwithstanding this appraisal, by many experts THC is recommended for the treatment of TS in adult patients, when first line treatments failed to improve the tics. In treatment resistant adult patients, therefore, treatment with THC should be taken into consideration.

Keywords: Tourette syndrome, tics, cannabinoids, cannabis sativa, THC

1. Introduction

Although the therapeutic spectrum in the treatment of Tourette syndrome (TS) has expanded during the last years, there is still a substantial number of patients who is unsatisfied with well established treatment strategies either due to less efficacy or significant adverse effects. In addition, there is still no therapy known that is not only effective in the treatment of tics, but also improves associated behavioural disorders. In those patients who are impaired not only by their tics, but also by psychiatric comorbidities combined treatment with several drugs is often inevitable [1]. Therefore, new therapeutic strategies are desirable that are more effective, cause less adverse effects, and ideally improve not only tics, but also associated behavioural problems. Against this background, many patients with TS seek alternative or complementary medicine including special diets and nutritional supplements [2,3] as well as legal and illegal drugs such as nicotine, alcohol and cannabis sativa [4, 5].

2. Medical use of cannabinoids

Cannabis has been used for medical purposes in many cultures for hundreds of years, in particular, for the treatment of pain, spasms, asthma, insomnia, depression, and loss of appetite. In the first half of the 20th century, cannabis-based medication almost completely lost its acceptation, among other things, because it did not succeed to identify the chemical structure of the ingredients of *Cannabis sativa* L. This situation changed in the 1960s, after the exact chemical structure of delta-9-tetrahydrocannabinol (THC), the most psychoactive ingredient of cannabis sativa, could be determined. Research on the medical use of cannabinoids was further stimulated when it became clear that cannabinoids act through specific receptors: a predominantly in the central nervous system located CB1 receptor and a CB2 receptor that is expressed primarily by immune tissues. In 1992, the first specific ligand that binds to cannabinoid receptors could be identified. To date, five different endocannabi-

noids are known, among them the two most important anandamide (arachidonoylethanolamide) and 2-arachidonoylglycerol (2-AG). There is substantial evidence that endocannabinoids affect the activity of excitatory neurotransmitters such as glutamate as well as inhibitory transmitters such as GABA and glycine, but also of several monoamines such as dopamine, serotonin, noradrenaline, acetylcholine, and neuropeptides (for review see [6]).

To day, in many countries the cannabinoid THC (dronabinol, nabilone) and the cannabis extract nabiximols (Sativex®) – containing THC:canabidiol (CBD) = 1:1 – are approved for clinical use for the treatment of nausea and vomiting associated with cancer chemotherapy, anorexia in HIV/AIDS, and spasticity in multiple sclerosis, respectively. However, there is substantial evidence that cannabinoids are also effective in the treatment of other conditions such as neuropathic pain, spasms and movement disorders (for review see [7]).

3. Anecdotal reports

In 1988, it has been suggested for the first time that use of smoked marijuana might be effective in the treatment of tics and behavioural symptoms in patients with TS. In a case study, Sandyk and Awerbuch [8] reported on three 15–39-year-old male patients who experienced an improvement of their tics and premonitory urges when smoking 1/2 to 2 marijuana cigarettes per day. In addition, the patients felt an improvement of self-mutilatory behaviour, attention span, and hypersexuality. In 1993, Hemming and Yellowlees [9] described a single case of a 36-year-old man with TS who reported that he had been symptom free for more than one year when taking one "cone" of marijuana per night.

In 1998, Müller-Vahl et al. [10] used a standardized questionnaire to perform a survey about the use of cannabis sativa and its effects on tics and psychiatric comorbidities in a larger group of TS patients. Of 64 consecutive adults who were interviewed, 17 reported about prior use of marijuana. Of these, 14 (82%) patients experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges, obsessive-compulsive behaviour (OCB), and attention deficit hyperactivity disorder (ADHD). None of these patients reported about serious adverse effects or a deterioration of symptoms while smoking marijuana.

4. Uncontrolled single case studies

Up to now, there are no controlled trials available investigating the effect of marijuana or a cannabis extract in TS. In Germany (and many other countries), until today the use of marijuana – even for medical purposes – is illegal. The cannabis extract nabiximols is available for medical use only for a few years. Thus, available clinical trials investigating the therapeutic effect of cannabinoids in TS used delta-9-tetrahydrocannabinol (THC), the most psychoactive ingredient of *cannabis sativa L.* However, it can be assumed that most clinical effects of cannabis sativa are caused by THC, although cannabis sativa contains more than 60 different cannabinoids.

In 1999, the effects of pure THC have been investigated in TS for the first time in a prospective open uncontrolled trial: a 25-year-old male patient was treated once with a single dose of 10 mg THC orally [11]. The patient reported that he had used marijuana (2–3 g per day) illegally for many years not only to reduce his tics, but also to improve behavioural problems including ADHD, OCB, anxiety, lack of impulse control, and self injurious behaviour, but stopped smoking marijuana 3 days before entering the study. Two hours after THC treatment the total tic severity score of the Tourette's Syndrome Global Scale (TSGS) [12] improved from 41 to 7 and coprolalia disappeared. No adverse effects occurred. Measuring cognitive functions neuropsychological tests showed improved signal detection, sustained attention, and reaction time after treatment. The patient felt not only a tic improvement of 70%, but also an amelioration in attention, impulse control, OCB, and premonitory urges.

In another open uncontrolled single case study investigating a 24-year-old female, a combined treatment with THC (10 mg/day) and amisulpride (1200 mg/day) was found superior compared to THC and amisulpride, respectively, alone [13]. Therefore, it can be speculated that THC augment anti-tic effects of dopamine receptor blocking drugs as suggested earlier by animal studies: In rats it has been demonstrating that haloperidol-induced hypokinesia significantly increases after co-administration of THC [14].

Brunnauer et al. [15] reported about a treatment resistant 42-year-old man whose tics decreased after treatment with 15 mg THC significantly (Yale Global Tic Severity Scale (YGTSS) [16] decreased from 89 to 22). Since he worked as a truck-driver, his driving ability was assessed using computerized tests to measure visual perception, reaction, concentration, and stress tol-

erance. Although the patient passed the test both in the drug-free phase and during THC treatment, his concentration and visual perception clearly improved after THC treatment. Thus, at least in patients with TS treatment with cannabinoids may result in improved driving ability.

A comparable observation has been made in a 28-year-old male suffering from ADHD (without tics) whose driving-related performance significantly improved after oral intake of THC [17]. The authors concluded that "... in persons with ADHD THC may have atypical and even performance-enhancing effects".

So far, there is only one single case report available describing the successful treatment of a 15-year-old boy with treatment refractory TS plus ADHD [18]. In this boy combined treatment with THC (up to 15 mg/day) plus aripiprazole (30 mg/day) and risperidone (3 mg/day) resulted not only in a marked tic reduction (YGTSS score decreased from 97 to 54), but also in an improvement in quality of life. No significant adverse effects occurred. Under THC treatment, for the first time, comedication with methylphenidate (30 mg/day) was well tolerated without tic exacerbation. Using transcranial magnetic stimulation (TMS), intracortical inhibition was found to be increased during THC treatment. The authors, therefore, suggested that THC might counteract deficits of intracortical inhibition in patients with TS and ADHD by modulating the release of several neurotransmitters including dopamine and F-aminobutyric acid.

5. Randomized controlled clinical trials

Until today, there are only two controlled trials available investigating the effects of orally administered pure THC in the treatment of TS. In a randomised double-blind placebo-controlled crossover single-dose trial 12 adult patients (11 men, 1 woman, mean age = 34 + 13 (SD) years, range, 18–66 years) were treated with 5, 7.5 or 10 mg THC (dosages were chosen according to patients' body weight, sex, age and prior use of marijuana) [19]. Patients were randomly assigned a single-dose of oral THC first or a single-dose of visually identical placebo first on two days separated by a 4-week washout phase. Using the self rating scale Tourette Syndrome Symptom List (TSSL) [20] a significant global tic improvement was found after THC compared with placebo ($p = 0.015$). In addition, a significant improvement of OCB ($p = 0.041$) could be assessed by TSSL. Using the examiner rating TSGS a significant improvement ($p = 0.015$) could be demonstrated for the subscore for complex motor tics. Data became more robust when including only those patients who had received 7.5 or 10.0 mg THC ($n = 8$) suggesting that higher dosages are more effective. All in all, 10/12 patients experienced a global improvement after THC (mean of + 35% ± 28.0, range, 20–90%), but only 3/12 after placebo (mean of + 7% ± 13.7, range, 10–40%).

In addition, the Symptom Checklist 90-R (SCL-90-R) [21] was used to evaluate different psychological symptoms. No influence of THC could be detected on depression, somatization, interpersonal sensitivity, anxiety, anger-hostility, paranoid ideation, and psychoticism, but there was evidence for a deterioration of OCB. From other studies, however, an improvement of OCB is suggested after treatment with cannabinoids [10,11].

No serious adverse reactions occurred. Five patients reported transient mild side effects after THC lasting between 1–6 hours (including headache, nausea, dizziness, hot flush, tiredness, poor powers of concentration, and cheerfulness). One patient reported dizziness, anxiety, tremble, sensitivity to noise and light, dry mouth, and ataxia after a single dose of 10 mg THC lasting half an hour.

In addition, a randomised double-blind parallel group placebo-controlled study over six-weeks has been performed including 24 adult patients with TS (19 men, 5 women, mean age = 33 + 11 (SD) years, range, 18–68 years) [22]. Starting at 2.5 mg THC/day the dosage was increased by 2.5 mg every four days to the target dosage of 10 mg. If a patient was unable to tolerate the maximum dose, the medication was reduced by up to 5.0 mg/day until a tolerated dose was achieved. The study consisted of 6 visits (visit 1 = baseline, visits 2–4 during treatment, visits 5 and 6 after withdrawal). Using the Global Clinical Impression Scale (GCIS) [20], at visits 3 and 4, respectively, a significant difference ($p < 0.05$) was found between the THC and placebo groups. Using ANOVA, there was a trend towards an overall significant difference ($p = 0.079$). Using the Shapiro Tourette Syndrome Severity Scale (STSS) [23], a significant group difference could be demonstrated ($p = 0.033$) at visit 4. At the same visit, both the subscore "motor global scale" of the YGTSS ($p = 0.040$) as well as the Rush videotape-based rating scale [24] ($p = 0.030$) demonstrated a significant difference between both groups. The self rating TSSL demonstrated a significant difference ($p < 0.05$) between the placebo and THC group on 10 treat-

ment days (between day 16 and 41). Using ANOVA there was an overall significant difference between the two groups ($p = 0.037$). Several other measures, in addition, demonstrated a trend ($p < 0.1$).

Seven patients dropped out of the study, but only one due to adverse effects (anxiety and restlessness). No serious adverse effects occurred. Five patients in the THC and three in the placebo group reported mild side effects (tiredness, dry mouth, dizziness, muzziness, anxiety, and depression).

6. Effects of cannabinoids on neuropsychological performance

The above mentioned controlled trials aimed to investigate the effect of THC not only on tics and associated behavioural problems, but also on neuropsychological performance. In the single-dose cross-over study a variety of neuropsychological tests was performed, but no detrimental effects of THC could be detected on short-term verbal and visual memory, recognition, verbal learning, intelligence, information processing, vigilance, reaction time, sustained attention and divided attention [25].

In the six-week parallel group study the following tests were performed to investigate cognitive functions: German version of the Auditory Verbal Learning Test (VLMT) [26], Benton-Visual-Retention-Test (BVRT) [27], Divided Attention (TAP) [28], and Multiple choice vocabulary test (Mehrfachwahl-Wortschatztest, MWT-B) [29]. Altogether – neither during treatment nor after withdrawal – no detrimental effects were seen on learning curve, interference, recall and recognition of word lists, immediate visual memory span, and divided attention. Measuring immediate verbal memory span there was even a trend towards an improvement during and after treatment with THC [30].

These results are in line with the case report by Brunnauer et al. [15] describing a truck-driver whose concentration and visual perception improved after THC treatment, but in contrast compared to data obtained from healthy cannabis users. In healthy users it has been demonstrated that cannabis use may cause cognitive impairment [31]. Since it can be speculated that the central cannabinoid system might be involved in the pathophysiology of TS, it is conceivable that treatment of THC in patients with TS may result in different effects on neuropsychological performance compared to healthy cannabis users.

7. Averse effects and contraindications

Based on available studies and case reports it can be assumed that adverse effects in patients with TS do not differ from adverse effects described in other groups of patients. It can be assumed that cannabis, cannabis extracts (such as nabiximols) and individual cannabinoid receptor agonists (such as dronabinol and nabilone) show very similar or even identical side effects. Cannabinoids are generally considered as well-tolerated. The American Institute of Medicine declared that "Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications" [32]. The most common side effects are tiredness and dizziness (in more than 10% of patients), psychological effects and dry mouth. Most commonly reported psychological effects are relaxation, euphoria, dysphoria, unpleasant feelings, heightened sensory and altered time perception, anxiety and panic (but also reduction of anxiety), impairment of memory, reductions in psychomotor and cognitive performance, and disorientation. Tolerance to these side effects nearly always develops within a short time. Most of the adverse effects can be prevented by slow and individual titration. In children and adolescents (but not in adults) there is substantial evidence that regular cannabis use at high doses may cause not only long-term effects on cognitive performance, but also doubles to risk of psychosis in vulnerable individuals [33,34]. Beside dry mouth other physical effects may occur such as tachycardia, orthostatic hypotension, reduced lacrimation, muscle relaxation, and increased appetite. Withdrawal symptoms are hardly ever a problem in the therapeutic setting [7].

Cannabinoids are contraindicated in patients suffering from a psychotic illness. THC should be used with caution in patients with a history of substance abuse, pregnant and breast feeding women, children < 18 years, and patients with significant cardiac disorder and hepatitis C [7].

8. The role of the CB1 receptor system in the pathophysiology of TS

Based on the beneficial effect of cannabinoids in the treatment of tics, it can be speculated that the central CB1 receptor system might be involved in the pathophysiology of TS. This hypothesis is supported

by the fact that the highest density of CB1 receptors is located in the basal ganglia, cerebellum, and hippocampus. In addition, there are several lines of evidence suggesting a complex interaction between the CB_1 receptor and the dopaminergic system. However, to date there is only one study available using the CB_1 antagonist [123I]AM281 (N-(Morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-[123I]iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide) and single photon emission computed tomography (SPECT) to investigate central cannabinoid CB_1 receptors in six patients with TS before and after THC treatment [35]. Although a specific binding of [123I]AM281 to CB_1 receptors could be detected, due to lack of a control group, no statement could be given as to whether CB_1 receptor binding sites are pathologically changed in TS. There is no evidence suggesting that TS is caused by genetic variations of the central cannabinoid receptor (CNR1) gene [36].

9. Conclusion and practical aspects

Available data obtained from several single case studies and two small controlled trials consistently provide evidence for beneficial effects of cannabinoids in the treatment of tics in patients with TS. In addition, there is some weak evidence that cannabinoids may improve also associated behavioural problems such as OCB, attention span, impulsivity, and autoaggression. Since neuropsychological tests failed to demonstrate detrimental effects of THC on memory, reaction time, concentration, and attention [15,25,30], it can be assumed that beneficial effects in patients with TS are caused by specific effects rather than secondary mechanisms due to sedation or decreased general activity. Since CB1 receptors are not only highly located in those brain regions that are thought to be involved in TS pathology, but also have a complex interaction with the dopaminergic system, it can be speculated that beneficial effects in TS are mediated directly though the central CB1 receptor system.

Limitations of the available studies that have to be addressed are the small sample size, short treatment period, large number of multiple comparisons, fixed dose approach, and possible selection bias. The authors of a recent Cochrane review [37] argued that definite conclusions on the efficacy of cannabinoids in TS cannot be drawn, because longer trials including a large number of patients are missing. Notwithstanding this appraisal, by many experts [1,37] THC is recommended for the treatment of TS in adult patients, when first line treatments failed to improve the tics. Thus, in treatment resistant adult patients therapy with THC should be taken into consideration.

Treatment with THC should be started at a low dose of 2.5 or 5 mg/day and slowly up titrated to a daily dose of 10–20 mg according to efficacy and tolerability. THC should be used twice or three times daily. From unpublished data, there is limited evidence that the cannabis extract nabiximols (Sativex®) – containing THC:CBD = 1:1 – can be used for the treatment of tics, too. Because costs for treatment with both THC and nabiximols are high and – at least in Europe – health insurances often refuse to cover these costs in patients with TS (due to lack of approval), in Germany patients can apply to the public authorities for a special approval for the use of medicinal cannabis [7]. From open uncontrolled case studies in a limited number of patients, it can be assumed that treatment with medicinal cannabis is also effective in TS, and in some patients even better tolerated than THC alone. Longer trials with larger numbers of patients are necessary to further establish the efficacy and safety of different cannabinoids in the treatment of TS.

References

[1] Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry. 2011; 20(4): 173-96.

[2] Mantel BJ, Meyers A, Tran QY, Rogers S, Jacobson JS. Nutritional supplements and complementary/alternative medicine in Tourette syndrome. J Child Adolesc Psychopharmacol. 2004; 14(4): 582-9.

[3] Müller-Vahl KR, Buddensiek N, Geomelas M, Emrich HM. The influence of different food and drink on tics in Tourette syndrome. Acta Paediatr. 2008; 97(4): 442–6.

[4] Müller-Vahl KR, Kolbe H, Dengler R. Alcohol withdrawal and Tourette's syndrome. Neurology. 1997; 48(5): 1478-9.

[5] Müller-Vahl KR, Kolbe H, Dengler R. [Gilles de la Tourette syndrome. Effect of nicotine, alcohol and marihuana on clinical symptoms]. Nervenarzt. 1997; 68(12): 985-9.

[6] Pertwee RG. Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addict Biol. 2008; 13(2): 147-59.

[7] Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int. 2012; 109(29–30): 495–501.

[8] Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. J Clin Psychopharmacol. 1988; 8(6): 444-5.

[9] Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. J Psychopharmacol. (Oxford) 1993; 7(4): 389-91.

[10] Müller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome. Acta Psychiatr Scand. 1998; 98(6): 502-6.

[11] Müller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. Am J Psychiatry. 1999; 156(3): 495.
[12] Harcherik DF, Leckman JF, Detlor J, Cohen DJ. A new instrument for clinical studies of Tourette's syndrome. J Am Acad Child Psychiatry. 1984; 23(2): 153-60.
[13] Müller-Vahl K, Schneider U, Emrich H. Combined treatment of Tourette-Syndrome with delts-9-THC and dopamine receptor antagonists. J Cannabis Therap. 2002; 2: 145-54.
[14] Moss DE, Manderscheid PZ, Montgomery SP, Norman AB, Sanberg PR. Nicotine and cannabinoids as adjuncts to neuroleptics in the treatment of Tourette syndrome and other motor disorders. Life Sci. 1989; 44(21): 1521-5.
[15] Brunnauer A, Segmiller FM, Volkamer T, Laux G, Müller N, Dehning S. Cannabinoids improve driving ability in a Tourette's patient. Psychiatry Res. 2011; 190(2–3): 382.
[16] Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989; 28(4): 566-73.
[17] Strohbeck-Kühner P, Skopp G, Mattern R. [Fitness to drive in spite (because) of THC]. Arch Kriminol. 2007; 220(1–2): 11-9.
[18] Hasan A, Rothenberger A, Münchau A, Wobrock T, Falkai P, Roessner V. Oral delta 9-tetrahydrocannabinol improved refractory Gilles de la Tourette syndrome in an adolescent by increasing intracortical inhibition: A case report. J Clin Psychopharmacol. 2010; 30(2): 190-2.
[19] Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002; 35(2): 57-61.
[20] Leckman J, Towbin K, Ort S, Cohen D. Clinical assessment of tic disorder severity. In: Cohen D, Bruun R, Leckman J, editors. Tourette's syndrome and tic disorders. New York: John Wiley; 1988.
[21] Derogatis LR, Lipman RS, Covi L. SCL-90: An outpatient psychiatric rating scale–preliminary report. Psychopharmacol Bull. 1973; 9(1): 13-28.
[22] Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003; 64(4): 459-65.
[23] Shapiro A, Shapiro E, Young J, Feinberg T. Signs, symptoms, and clinical course. In: Shapiro A, Shapiro E, Young J, Feinberg T, editors. Gilles de la Tourette Syndrome. 2nd ed. New York: Raven Press; 1988; p. 127-93.
[24] Goetz CG, Tanner CM, Wilson RS, Shannon KM. A rating scale for Gilles de la Tourette's syndrome: description, reliability, and validity data. Neurology. 1987; 37(9): 1542-4.
[25] Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry. 2001; 34(1): 19-24.
[26] Helmstaedter C, Lendt M, Lux S. VLMT – verbaler Lern- und Merkfähigkeitstest. Beltz Test GmbH, Hogrefe Verlag; 2001.
[27] Benton AL. A visual retention test for clinical use. Arch Neurol Psychiatry. 1945; 54: 212-6.
[28] Zimmermann P, Fimm B. Neuropsychologische Testbatterie zur Erfassung von Aufmerksamkeitsdefiziten. Psychologisches Institut der Universität Freiburg; 1989.
[29] Merz J, Lehrl S, Galster J, Erzigkeit H. MWT-B – ein Intelligenzkurztest. Psychiatr Neurol Med Psychol. 1975; 27: 423-8.
[30] Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology. 2003; 28(2): 384-8.
[31] Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: A review. Curr Drug Abuse Rev. 2008; 1(1): 81-98.
[32] Joy B, Watson SJ, Benson JA, Jr. Marijuana and Medicine. Division of Neuroscience and Behavioral Health [Internet]. Washington, D.C.: National Academy Press; 1999 [cited 2012 Sep 7]. Available from: http://www.nap.edu/openbook.php?record_id=6376.
[33] Klosterkötter J. Indicated prevention of schizophrenia. Dtsch Arztebl Int. 2008; 105(30): 532-9.
[34] Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RSE, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc. Natl. Acad. Sci. U.S.A. [Internet]. 2012 Aug 27 [cited 2012 Sep 11]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22927402.
[35] Berding G, Müller-Vahl K, Schneider U, Gielow P, Fitschen J, Stuhrmann M, et al. [123I]AM281 single-photon emission computed tomography imaging of central cannabinoid CB1 receptors before and after Delta9-tetrahydrocannabinol therapy and whole-body scanning for assessment of radiation dose in tourette patients. Biol Psychiatry. 2004; 55(9): 904-15.
[36] Gadzicki D, Müller-Vahl KR, Heller D, Ossege S, Nöthen MM, Hebebrand J, et al. Tourette syndrome is not caused by mutations in the central cannabinoid receptor (CNR1) gene. Am J Med Genet B Neuropsychiatr Genet. 2004; 127B(1): 97-103.
[37] Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's Syndrome. Cochrane Database Syst Rev. 2009; (4): CD006565.
[38] Pringsheim T, Doja A, Gorman D, McKinlay D, Day L, Billinghurst L, et al. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. Can J Psychiatry. 2012; 57(3): 133-43.