Tourette Syndrome Deep Brain Stimulation: A Review and Updated Recommendations

Lauren E. Schrock, MD,1 Jonathan W. Mink, MD, PhD,2 Douglas W. Woods, PhD,3 Mauro Porta, MD,4 Dominico Servello, MD,5 Vetrie Visser-Vandewalle, MD, PhD,6 Peter A. Silburn, MD,7 Thomas Foltynie, MRCP, PhD,8 Harrison C. Walker, MD,9 Joohi Shahed-Jimenez, MD,10 Rodolfo Savica, MD,11 Bryan T. Kisslen, MD,11 Andre G. Machado, MD,12 Kelly D. Foote, MD,13 Jian-Guo Zhang, MD, PhD,14 Wei Hu, MD, PhD,11,14 Linda Ackermans, MD, PhD,15 Yasin Temel, MD, PhD,15 Zoltan Mari, MD,16 Barbara K. Changizi, MD,17 Andres Lozano, MD,18 M. Auyeung, MD,19 Takanobu Kaido, MD, PhD,20 Yves Agid, MD, PhD,21 Marie L. Weiler, MD, PhD,22 Suketu M. Khandhar, MD,22 Alon G. Mogilner, MD, PhD,24 Michael H. Pourfar, MD,24 Benjamin L. Walter, MD,24 Jorge L. Juncos, MD,26 Robert E. Gross, MD,27 Jens Kuhn, MD,28 James F. Leckman, MD,29 Joseph A Neimat, MD,30 Michael S. Okun, MD,31 on behalf of the and Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group

1Department of Neurology, University of Utah, Salt Lake City, Utah, USA
2Department of Neurology, University of Rochester Medical Center, Rochester, New York, USA
3Department of Psychology, Texas A&M University, College Station, Texas, USA
4Tourette Centre, IRCCS Galeazzi Hospital, Milan, Italy
5Functional Neurosurgical Unit, IRCCS Galeazzi Milano, Milan, Italy
6Department of Stereotactic and Functional Neurosurgery, University of Cologne, Cologne, Germany
7Royal Brisbane and Women’s Hospital, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
8University College London Institute of Neurology, London, United Kingdom
9Department of Neurology, University of Alabama Birmingham, Birmingham, Alabama, USA
10Department of Neurology, Baylor College of Medicine, Houston, Texas, USA
11Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA
12Center for Neurological Restoration, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
13Departments of Neurology, Neuropsychology, and Psychiatry, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, Florida, USA
14Department of Neurosurgery, Beijing Tiantan Hospital, Capital University of Medical Sciences, Beijing, China
15Department of Neurosurgery, Maastricht University Medical Center, The Netherlands
16Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA
17Departments of Neurology and Psychiatry, The Ohio State University Wexner Medical Center, Ohio, USA
18Division of Neurosurgery, University of Toronto, Toronto, Ontario, Canada
19Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong, SAR China
20Department of Neurosurgery, National Center Hospital, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan
21Institut du Cerveau et de la Moelle Epinière (ICM), CHU Pité-Salpêtrière, Paris, France
22Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière (CRICM), Université Pierre et Marie Curie-Paris 6, Paris, France
23Northern California Kaiser Permanente, Surgical Movement Disorders Program, Sacramento, California, USA
24Departments of Neurosurgery and Neurology, New York University, Langone Medical Center, New York, New York, United States of America
25Movement Disorders Center, Neurological Institute, University Hospitals and Case Western Reserve University School of Medicine, South Euclid, Ohio, USA
26Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA
27Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia, USA
28Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany
29Child Study Center and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut, USA
30Department of Neurological Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA

*Correspondence to: Michael S. Okun, MD, 3450 Hull Road, Department of Neurology, Center for Movement Disorders and Neurorestoration, Gainesville, FL 32607, E-mail: okun@neurology.ufl.edu

Funding agencies:

Relevant conflicts of interest/financial disclosures: Nothing to report.

Author roles may be found in the online version of this article.

Received: 4 April 2014; Revised: 6 October 2014; Accepted: 8 October 2014

Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26094
ABSTRACT: Deep brain stimulation (DBS) may improve disabling tics in severely affected medication and behaviorally resistant Tourette syndrome (TS). Here we review all reported cases of TS DBS and provide updated recommendations for selection, assessment, and management of potential TS DBS cases based on the literature and implantation experience. Candidates should have a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) diagnosis of TS with severe motor and vocal tics, which despite exhaustive medical and behavioral treatment trials result in significant impairment. Deep brain stimulation should be offered to patients only by experienced DBS centers after evaluation by a multidisciplinary team. Rigorous preoperative and postoperative outcome measures of tics and associated comorbidities should be used. Tics and comorbid neuropsychiatric conditions should be optimally treated per current expert standards, and tics should be the major cause of disability. Psychogenic tics, embellishment, and malingering should be recognized and addressed. We have removed the previously suggested 25-year-old age limit, with the specification that a multidisciplinary team approach for screening is employed. A local ethics committee or institutional review board should be consulted for consideration of cases involving persons younger than 18 years of age, as well as in cases with urgent indications. Tourette syndrome patients represent a unique and complex population, and studies reveal a higher risk for post-DBS complications. Successes and failures have been reported for multiple brain targets; however, the optimal surgical approach remains unknown. Tourette syndrome DBS, though still evolving, is a promising approach for a subset of medication refractory and severely affected patients. © 2014 International Parkinson and Movement Disorder Society

Key Words: Tourette syndrome; DBS; guidelines; deep brain stimulation

Tourette syndrome (TS) is a chronic neurodevelopmental disorder characterized by motor and phonic tics that by definition occur with a childhood onset.1 The syndrome is commonly associated with other neuropsychiatric comorbidities (eg, attention deficit hyperactivity disorder [ADHD], obsessive compulsive features [OCD], and other behavioral manifestations). In most TS cases, the motor manifestations can be managed using TS education, comprehensive behavioral intervention for tics (CBIT), or a variety of medications.2-4 The natural history of TS is that most patients will experience improvement of tics in late adolescence or early adulthood.5,6 However, a subset of patients will continue to experience disabling tics despite optimal medication and behavioral management. For severely affected patients, deep brain stimulation (DBS) has the potential to improve refractory and disabling symptoms.

Methods

An experienced group of physicians participating in the Tourette Syndrome Association (TSA) International DBS Database/Registry, and also actively involved in managing TS DBS patients, reviewed the 2006 TSA guidelines7 and examined all reported cases of TS DBS. The TSA Database/Registry group accepted complete information sets on outcomes from TS DBS (database entry), as well as registration of cases performed with or without outcome information (registry entry). The group summarized the literature (Table 1) and based on their collective experience with TS DBS provided suggested updates (Table 2) and a consensus opinion on the TSA recommendations put in place in 2006.7

Literature Review

Deep brain stimulation is an established treatment for Parkinson’s disease (PD),8-12 essential tremor,13,14 dystonia,15-17 and obsessive-compulsive disorder,18,19 and has been granted either full Food and Drug Administration (FDA) approval (PD, essential tremor), or a humanitarian device exemption (FDA; dystonia, OCD) for each of these indications (in the United States). Many studies and position papers detail careful and meticulous techniques for screening patients for DBS,13,16,20-22 including a few reports for TS patients.23,24 General guidelines for selecting individual TS patients for DBS therapy and for managing them preoperatively and postoperatively will have the potential to improve risk–benefit ratios. The importance of rigorous preoperative assessment, patient selection, DBS team expertise and experience, as well as postoperative management has been demonstrated previously, especially when groups have studied cohorts of patients who have failed DBS therapy.25,26 Because TS is a childhood-onset disorder, often with complex clinical features, a waxing and waning course, and frequent neuropsychiatric comorbidities, the evaluation of patients has a greater level of complexity than many of the other current DBS indications.

In 2005, the TSA hosted a meeting of physicians with experience and expertise in TS and DBS to
### Table 1. Review of reported TS DBS cases

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size (n)</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Servello et al., 2008&lt;sup&gt;69&lt;/sup&gt;</td>
<td>CM-Pfc, Voa</td>
<td>18 (15M, 3F)</td>
<td>17–47</td>
<td>8 (2 ≤ 18 yrs)</td>
<td>3–18 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS; 64.7% mean improvement</td>
<td>None reported</td>
<td>Yes (9 with SIB; 3 No cervical myelopathy, 1 disc herniation, 2 unable to eat)</td>
<td></td>
<td>1. Transient stim-induced vertigo &amp; visual AE 2. Poor scalp incision healing due to repetitive touching; body shield required (n = 1) 3. Abdominal hematoma (n = 1) 4. Frequent programming required in many 1. 3 pts from previous cohort (n = 18) were excluded: 2 pts requested removal of IPG and DBS was stopped 1 pt did poorly and required subsequent GPi DBS</td>
</tr>
<tr>
<td>Porta et al., 2009&lt;sup&gt;70&lt;/sup&gt;</td>
<td>CM-Pfc, Voa</td>
<td>15 (12M, 3F); *all previously reported&lt;sup&gt;62&lt;/sup&gt;</td>
<td>17–46</td>
<td>7 (2 ≤ 18 yrs)</td>
<td>24 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS; 52% mean improvement</td>
<td>1. Y-BOCS; 31% mean improvement</td>
<td>Yes</td>
<td>No</td>
<td>1. Decreased energy levels, subjective gaze disturbance, negative impact on daily living in all pts 2. 1 small hemorrhage at lead tip—gaze palsy 3. 1 IPG Infection 4. Severe complications, psychogenic symptoms, &amp; eventual death in 1 pt lost to follow-up (see details below&lt;sup&gt;40&lt;/sup&gt;) 1. Severe postoperative complications with psychogenic paroxysmal hypertonia, disturbances of consciousness, and mutism 2. No change with DBS OFF</td>
</tr>
<tr>
<td>Ackermans et al., 2011&lt;sup&gt;70&lt;/sup&gt;</td>
<td>CM-Spv-Voi</td>
<td>8 (2F, 6M); *2F lost to follow-up</td>
<td>21–48</td>
<td>1 (21)</td>
<td>12 mo</td>
<td>Double-blind randomized cross-over trial × 6 mo, then 6 mo open-label</td>
<td>III</td>
<td>1. YGTSS; 49% improvement 2. mR/TRS; 35% improvement</td>
<td>1. Y-BOCS—no change 2. CAARS—no change 3. BDI (Dutch)—no change 4. VAS subjective social impairment—no change</td>
<td>Yes</td>
<td>Yes</td>
<td>1. Life-threatening, lost to follow-up</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size (n)</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ackermans 2007</td>
<td>CM-Spv-Voi 1 (M)</td>
<td>1 (M) *previously reported&lt;sup&gt;35&lt;/sup&gt;</td>
<td>39</td>
<td>0</td>
<td>6 mo</td>
<td>Case report</td>
<td>IV</td>
<td>NA</td>
<td>None reported</td>
<td>Yes (head-banging)</td>
<td>No</td>
<td>1. Hemorrhage at distal electrode tip -&gt; vertical gaze palsy; subjective worsening with DBS ON</td>
</tr>
<tr>
<td>Ackermans et al., 2006</td>
<td>CM-Spv-Voi 1 (M)</td>
<td>1 (M) *previously reported&lt;sup&gt;35&lt;/sup&gt;</td>
<td>45</td>
<td>0</td>
<td>1 yr</td>
<td>Case report</td>
<td>IV</td>
<td>1. Videotaped tic frequency (tics/min) by 2 blinded raters 85% reduction</td>
<td>1. Padua Inventory—Revised (obsession-compulsion rating) 62% better ON than OFF stim</td>
<td>No</td>
<td>No</td>
<td>1. Decreased energy level 2. Sexual dysfunction</td>
</tr>
<tr>
<td>Vandewalle et al., 1999</td>
<td>CM-Spv-Voi 1 (M)</td>
<td>1 (M)</td>
<td>42</td>
<td>0</td>
<td>4 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. Videotaped tic frequency —Nearly 100% reduction (&quot;except for some excessive eye blinking&quot;)</td>
<td>None reported</td>
<td>No</td>
<td>No</td>
<td>Not reported</td>
</tr>
<tr>
<td>Visser-Vandewalle et al., 2003</td>
<td>CM-Spv-Voi 3 (3M); *1M previously reported&lt;sup&gt;37&lt;/sup&gt;</td>
<td>3 (3M)</td>
<td>28,42,45</td>
<td>0</td>
<td>8 mo—5 yrs</td>
<td>Case series</td>
<td>IV</td>
<td>1. Videotaped tic frequency (tics/10min) —72%—90% reduction</td>
<td>None reported</td>
<td>No (burning eye-lashes with cigarettes, breaking glass in hands)</td>
<td>No</td>
<td>1. Reduced energy levels in all 3 2. Sexual dysfunction in 2 pts 3. 2 pts each required 3 revisions of IPG and extension wires due to traction pain 4.1 pt had lower scores on timed tasks on neuropsychological testing</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size (n)</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
</table>
| Ackermans et al., 2010        | CM-Spv-Voi 2       | 2 (2M); *previ-42, 45 yrs reported* | 0                 | 6–10 yrs               | Case reports | IV           | 1. Videotaped tic frequency (tics/10min) by 3 blinded raters | 78%-92.6% reduction | None reported | No (breaking glass) | No (in hands) | 1. Reduced energy levels in both pts  
2. Both with hardware-related complications (traction of lead in neck) requiring multiple surgical revisions and local injections (previously described)  
3. Mild visual side effects (vertigo, blurry vision) in both  
4. Sexual dysfunction in both  
5. Increased aggression, social adaptation in 1 pt. |
| Maciunas et al., 2007         | CM-Pf 5 (4M, 1F)   | 18–34           | ≥ 1                | 4 mo                    | Prospective double-blind crossover trial; four 7-d randomized DBS conditions RVL, ON/OFF, and open-label 4-mo follow-up | III         | 1. mRVTRS 40%-67% mean motor tic reduction  
2. YGTSS 43.6% mean improvement  
3. TSSL 43% mean reduction  
4. Tic Outcome Measures | 1. SF-36 (19% mean improvement)  
2. VAS (53% mean improvement)  
3. BDI-2* (60% mean improvement)  
4. HAM-D* (29% mean improvement)  
5. HAM-A* (51% mean improvement)  
6. Y-BOCS* (44% mean improvement) | Not reported | Yes (only mean coordinates provided) | 1. 1 pt had acute psychosis on day 28 of randomized phase—thought to be related to acute life stressors |
| Bajwa et al., 2007            | CM-Spv-Voi 1       | 1 (M)           | 0                 | 2 yrs                   | Case report  | IV           | 1. Y-BOCS 72.4% improvement  
2. CGI “very much improved” | Yes (head-snap ping tics causing cervical myelopathy) | No | 1. Although tics dramatically reduced, the head-snapping tics had only mild reduction in forcefulness and he had continued neurological deterioration due to myelopathy |

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size (n)</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shields et al., 2008(^6)</td>
<td>CM* (AUC leads previously removed)</td>
<td>1 (f)</td>
<td>40</td>
<td>0</td>
<td>3 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 46% improvement</td>
<td>None reported</td>
<td>Yes (head-snap-(p)ping tics, limb fractures, retinal detachment)</td>
<td>No</td>
<td>1. High stimulation settings required causing IPG depletion q1–2 yrs</td>
</tr>
<tr>
<td>Savica et al., 2012(^5)</td>
<td>CM-Pf</td>
<td>3 (2M, 1F)</td>
<td>17–35</td>
<td>2 (17,17)</td>
<td>1 yr</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 70% mean improvement</td>
<td>None reported</td>
<td>Yes (jaw-clenching causing dental fractures; head-snapping tics)</td>
<td>No</td>
<td>1. Mild stimulation-related adverse effects amenable to programming changes</td>
</tr>
<tr>
<td>Idris et al., 2010(^3)</td>
<td>CM-Pf, Voa</td>
<td>1 (M)</td>
<td>24</td>
<td>1</td>
<td>2 mo</td>
<td>Case report</td>
<td>IV</td>
<td>No scales reported (tics noted to improve)</td>
<td>None reported</td>
<td>No</td>
<td>No</td>
<td>1. Postoperative bilateral subcortical hematomas attributed to low factor XIIA</td>
</tr>
<tr>
<td>Marceglia et al., 2010(^5)</td>
<td>CM-Pf, Voa</td>
<td>7 (6M, 1F)</td>
<td>24–52</td>
<td>1 (24)</td>
<td>6 mo-2 yr</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 33% mean improvement (10%-49%) 1. Y-BOCS (3% mean improvement; 24% improvement to 47% worsening) 2. BDI (7% mean improvement) 3. STAI (20% mean improvement) 4. 10-pt VAS of social integration (14% mean improvement) 1. Y-BOCS 17.3% improvement at last f/u ((p = .017)) 2. BDI 32.4% improvement at last f/u ((p &lt; 0.001)) 3. STAI 31.7% improvement at last f/u ((p &lt; 0.002)) 4. 10-pt VAS of social integration 30.7% improvement at last f/u ((p &lt; 0.001))</td>
<td>No reported</td>
<td>No</td>
<td>1. Infection of IPG/extension requiring system removal (n = 1) 2. Infection of IPG site requiring revision (n = 2) 3. Wound revision along lead extensions due to picking behavior (n = 2) 4. Lead revision (\times) 2 in 1 patient 5. Rupture of lead extension (n = 1) 6. IPG removed @ 27 mo at pt request due to unsatisfactory results + aes-thetic concerns (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Servello et al., CM-Pfc, Voa (1 unilateral, excluded from analysis)</td>
<td>31 (25M, 6F); (\sim 18) previously reported (62) (4 additional pts received leads in multiple targets &amp; 1 in ALIC/NA only)</td>
<td>17–57</td>
<td>11</td>
<td>3 mo-4 yr</td>
<td>Case series (36 pt IV cohort; 6 excluded from analysis due to &lt;3 mo f/u or non-thalamic target)</td>
<td>1. YGTSS 47% mean improvement at last f/u ((p &lt; 0.001))</td>
<td>Yes (2 with cervical myelopathy, 1 with collapsed trachea, from tics)</td>
<td>1. Infection of IPG/extension requiring system removal (n = 1) 2. Infection of IPG site requiring revision (n = 2) 3. Wound revision along lead extensions due to picking behavior (n = 2) 4. Lead revision (\times) 2 in 1 patient 5. Rupture of lead extension (n = 1) 6. IPG removed @ 27 mo at pt request due to unsatisfactory results + aesthetic concerns (n = 1)</td>
<td>(Continued)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target</td>
<td>Sample size</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
<td>Level of Evidence</td>
<td>Tic Outcome Measures</td>
<td>Comorbidity</td>
<td>SIB With Immediate Risk of Bodily Harm (Yes/No)</td>
<td>Postoperative Lead Location Reported (AC-PC Coordinates)</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>-------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Porta et al., 2012</td>
<td>CM-Pfc, Vba</td>
<td>18 (3F, 15M); previously reported(62)</td>
<td>17–47</td>
<td>8 5–6 yrs</td>
<td>Case series IV</td>
<td>1. YGTSS 73% mean improvements ($p &lt; 0.001$) 2. GG—ratings varied between providers and between provider and patients 1. Y-BDCS 42% mean improvement ($p = 0.003$) (4 pts worsened) 2. STAI 46% mean improvements ($p &lt; 0.001$) 3. BDI 55% mean improvement ($p &lt; 0.001$)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuhn et al., 2011</td>
<td>Vop-Voa-Voi (Unilateral)</td>
<td>2 27 (F); 39 (M)</td>
<td>0 12 mo</td>
<td>Case series IV</td>
<td>1. YGTSS 75%-100% improvement 2. MIVRS 77%-100% improvement 1. Y-BOCS 2. HDRS</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2011</td>
<td>CM-Pf</td>
<td>1 31 (M)</td>
<td>0 18 mo</td>
<td>Case report IV</td>
<td>1. YGTSS 62% improvement @ 6 mo (sustained at 18 mo) 2. MIVRS 38% improvement 3. VAS 70% improvement</td>
<td>Yes reported</td>
<td>Yes</td>
<td>No</td>
<td>1. Reduced verbal fluency @1 yr in both pts (~25% worsening)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okun et al., 2012</td>
<td>CM (scheduled 5 (3F, 2M) stimulation)</td>
<td>28–39</td>
<td>0 6 mo</td>
<td>NIH-sponsored clinical trials planning study of safety and preliminary efficacy; delayed start activation (30d) 1. YGTSS 19% mean improvement ($p = 0.01; 5%-30$) 2. MIVRS 36% mean improvement ($p = 0.01$) 1. Y-BDCS 2. HDRS 3. YMRS (Young Mania Rating Scale 4. SF-36 5. QOLAS</td>
<td>Yes (3 of 5 pts)</td>
<td>Yes</td>
<td>1. No major adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target</td>
<td>Sample size (n)</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
<td>Level of Evidence</td>
<td>Tic Outcome Measures</td>
<td>Comorbidity Outcome Measures</td>
<td>SIB With Immediate Risk of Bodily Harm (Yes/No)</td>
<td>Postoperative Lead Location Reported (AC-PC Coordinates)</td>
<td>Adverse Events Reported</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Kuhn et al., 2012&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Thalamus, pallidal, &amp; nigral input areas (unilateral in 1)</td>
<td>3 (2M, 1F)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22–27</td>
<td>2 (22, 22)</td>
<td>NA</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS—36%-83% improvement</td>
<td>None reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>None reported</td>
</tr>
<tr>
<td>Vernaleken et al., 2009&lt;sup&gt;49&lt;/sup&gt;</td>
<td>PF-DM-LM</td>
<td>1 (M)</td>
<td>22</td>
<td>1</td>
<td>NA</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS—36% improvement</td>
<td>None reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>1. Patient had previously undergone bilateral GPI DBS without improvement</td>
</tr>
<tr>
<td>Servello et al., 2011&lt;sup&gt;64&lt;/sup&gt;</td>
<td>NA</td>
<td>39,* most previously reported(64)</td>
<td>NA</td>
<td>Retrospective review</td>
<td>IV</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1. Lead fracture due to head-snapping tics 2. 18% incidence of infectious complications (7 patients), requiring surgical revision 3. All 7 patients with infections had recurrent infection 4. Infections thought related to compulsive touching of surgical scars</td>
<td>1. Temporary blurred vision with increased stimulation amplitude</td>
<td></td>
</tr>
<tr>
<td>Kaido et al., 2011&lt;sup&gt;44&lt;/sup&gt;</td>
<td>CM-Pfc</td>
<td>3 (1M, 2F)</td>
<td>19–21</td>
<td>3 (20, 21, 19)</td>
<td>12 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS—39.1% mean improvement 1. Y-BOCS—slight decrease in 2 pts, increase in 1 pt 2. BDHI—varied between patients 3. IQ—no significant mean change</td>
<td>Yes (2 of 3 pts)</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motlagh et al., Midline thalamic 2013&lt;sup&gt;33&lt;/sup&gt;</td>
<td>4M</td>
<td>16–44</td>
<td>2 (16, 17)</td>
<td>6–95 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS—dramatic improvement in the 2 young pts (67%-85%); limited improvement in the older pts (7%-20%) 1. Y-BOCS—100% improvement in 1 pt; minimal change or worsening in the others 2. HDRS and HARS—no significant change</td>
<td>Yes (2 of 4 pts)</td>
<td>Yes</td>
<td>1. 44-yo M had compulsive picking at chest and cranial incisions; DBS system removed because of infection 2. 42-yo M had DBS system removed because of lack of therapeutic benefit</td>
<td>(Continued)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target</td>
<td>Sample size (n)</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
<td>Study Target</td>
<td>Sample size (n)</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-----------------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Diederich et al., 2005</td>
<td>pvGPi</td>
<td>1</td>
<td>27 (M)</td>
<td>0</td>
<td>14 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. Videotaped tic frequency (tics/min) 85% reduction (66% increase with DBS OFF) 2. YGTSS 47.0% improvement</td>
<td>1. BDI (75% improvement) 2. STAI (30% improvement) 3. SRSI-90-R (31%-61% improvement)</td>
<td>No</td>
<td>No</td>
<td>1. Permanent left-sided bradykinesia (grade 2–3 on UPDRS)—tolerated by pt; reduced mildly with stimulation OFF × 48 hr 2. Small non–mass-occupying hematoma @ tip of R electrode on post-op MRI 3. Transient mild fatigue for several months</td>
</tr>
<tr>
<td>Shahed et al., pvGPi</td>
<td>pvGPi</td>
<td>1 (M) *also reported (66)</td>
<td>16</td>
<td>1</td>
<td>6 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 84% improvement 2. TSSR 88% improvement 3. mRVTRS 21% improvement</td>
<td>1. Children’s Y-BOCS (69% improvement) 2. SF-36 v2 (65% improvement) 3. BASC-2 (improvements in several domains, including hyperactivity, aggression, anxiety, depression, somatization)</td>
<td>No</td>
<td>No</td>
<td>1. Patient compulsively pushed on IPGs, requiring body shield for 4 wks</td>
</tr>
<tr>
<td>Shahed et al., pvGPi</td>
<td>pvGPi</td>
<td>3</td>
<td>3M (16–35)</td>
<td>2 (16,16)</td>
<td>3–12 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 35%-76% improvement 2. TSSR 16%-90% improvement 3. RVTRS 17%-50% improvement 4. Tic frequency (tics/min) 37%-69% reduction</td>
<td>1. Y-BOCS (22%-69% improvement)</td>
<td>Not reported</td>
<td>No</td>
<td>1. No surgical adverse events. 2. 1 patient compulsively pushed on the IPG site.</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehning et al., pvGPi 2008</td>
<td>pvGPi</td>
<td>1</td>
<td>44 (F)</td>
<td>0</td>
<td>12 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 88% improvement; no remaining tics</td>
<td>None reported</td>
<td>No (self-biting, beating)</td>
<td>Yes</td>
<td>1. Frequent visits in 1st few months for depression, vertigo, stomach aches; difficulty adjusting to new situation without tics. 2. Lead revision to a more posterior location was done in 1 nonresponder, without improvement</td>
</tr>
<tr>
<td>Dehning et al., pvGPi 2011</td>
<td>pvGPi 4; *1 previously reported(35)</td>
<td>3F (25–44); 1M (38)</td>
<td>0</td>
<td>5–13 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 6% worsening to 88% improvement 2. CGI 67% mean improvement (including 2 with no change) 3. TSQS 12% worsening to 80% improvement (mean 37%)</td>
<td>None reported</td>
<td>Yes (burning of skin with iron)</td>
<td>No</td>
<td>1. Stimulation stopped due to lack of response (n = 2) 2. Lead revision to a more posterior location was done in 1 nonresponder, without improvement</td>
<td></td>
</tr>
<tr>
<td>Dong et al., pvGPi (unilateral R) 2012</td>
<td>pvGPi</td>
<td>2</td>
<td>2 M (22, 41)</td>
<td>1 (22)</td>
<td>1 year</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 53%-59% improvement 2. CGI 67% mean improvement (including 2 with no change) 3. TSQS 12% worsening to 80% improvement (mean 37%)</td>
<td>None reported</td>
<td>No</td>
<td>No</td>
<td>1. No severe adverse effects</td>
</tr>
<tr>
<td>Dueck 2009</td>
<td>pvGPi</td>
<td>1</td>
<td>16 (M)</td>
<td>1 (16)</td>
<td>1 year</td>
<td>Case report</td>
<td>IV</td>
<td>Y-BOCS (26% mean reduction) Reported no associated psychiatric symptoms</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Gallagher 2006</td>
<td>pvGPi</td>
<td>1</td>
<td>26 (M)</td>
<td>0</td>
<td>NA</td>
<td>Case report</td>
<td>IV</td>
<td>NA</td>
<td>None reported</td>
<td>No</td>
<td>1. No severe adverse effects</td>
<td></td>
</tr>
<tr>
<td>Martinez-Fernandez 2011</td>
<td>pvGPi (3); amGPi (3)</td>
<td>5</td>
<td>4M(21–60); 1F (21)</td>
<td>3–24 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 29% mean improvement 2. mRVTRS 45% mean improvement Impression: amGPi is superior to pvGPi (YGTSS 38% vs. 20% improvement; mRVTRS 54% vs. 37%)</td>
<td>1. Y-BOCS (26% mean reduction) 2. GTS-QOL (55% mean improvement; available in 3 pts) 3. GTS-QOL VAS—40 points mean improvement (total 100)</td>
<td>Yes (2 with cervical myelopathy from head-snap ting tics)</td>
<td>No</td>
<td>1. Two infections in 1 patient (requiring system removal × 1, IPG/extension removal × 1) 2. Lethargy, agitation, anxiety; unhappy with results despite reduced tics (n = 1) 3. Low threshold capsular side effects; lead revision to anteromedial target, then anxiety with &gt;100 Hz stimulation</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Target</th>
<th>Sample size</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al., amGPi 2012</td>
<td>Thalamic</td>
<td>11</td>
<td>8M (22–50); 3F (18–22)</td>
<td>4–30 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS 50% mean reduction @ 3 mo</td>
<td>1. Y-BOCS (59% mean improvement)</td>
<td>2. HDRS (74% mean improvement)</td>
<td>3. GTS-QLS—significant improvement (102% mean improvement)</td>
<td>4. GAF (57% mean improvement)</td>
<td>Yes (requiring 24-hr monitoring to prevent head injury)</td>
</tr>
<tr>
<td>Filho et al., 2007</td>
<td>GPe</td>
<td>1</td>
<td>NA</td>
<td>23 mo</td>
<td>Case report (abstract only)</td>
<td>IV</td>
<td>1. YGTSS—81% reduction</td>
<td>1. Y-BOCS—84% reduction</td>
<td>2. HDRS (71% improvement @ 6 mo)</td>
<td>3. GTS-QLS—significant worsening @ 2 yr when IPG battery died</td>
<td>4. GAF—(56% improvement @ 6 mo)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Piedimonte et al., 2013</td>
<td>GPe</td>
<td>1</td>
<td>47 (M)</td>
<td>0</td>
<td>2 yrs</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS—81% reduction</td>
<td>1. Y-BOCS—84% reduction</td>
<td>2. HDRS (82% improvement @ 6 mo)</td>
<td>3. GTS-QLS—significant worsening @ 2 yr when IPG battery died</td>
<td>4. GAF—(56% improvement @ 6 mo)</td>
</tr>
<tr>
<td>Motlagh et al., pvGPi 2013</td>
<td>Thalamic</td>
<td>2</td>
<td>2M (24, 42); 1 (24)</td>
<td>8–51 mo</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS—20%–44% improvement</td>
<td>1. Y-BOCS—no significant change</td>
<td>2. HDRS—no change to mild improvement</td>
<td>3. GTS-QLS—significant improvement</td>
<td>Yes (2 of 2; 1 transient, 1 persistent &amp; fluctuating)</td>
<td>Yes (2 of 2; punching self, neck-snapping tics + cervical spine injury)</td>
</tr>
</tbody>
</table>

4. Acute deterioration in tics with transient stim OFF—only 70% of previous control after back ON 5. Weight gain (n = 1) 1. One pt did not tolerate DBS and turned OFF after 3 mo because of somatic complaints 2. Hardware malfunction (lead fracture) in 3 pts (because of: SIB tic, MVA, unknown) 3. Lead infection requiring bilateral lead replacement (n = 1) 4. Increased anxiety in 2 pts (1 transient, 1 persistent, & fluctuating) Not reported

4. Lead extender revision due to post-auricular discomfort, possible IPG malfunction with revision to abdominal placement 2. Stimulation-induced side effects: hyperkinetic left arm movement, right foot cramping, flashing in eyes, restlessness; Left lead quite medial.
### TABLE 1. Continued

**Target: Thalamic**

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size (n)</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Servello et al., 2009&lt;sup&gt;56&lt;/sup&gt;</td>
<td>CM-Pfc, Voa + ALIC/NA (n = 1); CM-Pfc, Voa + ALIC/NA add-on (n = 2)</td>
<td>3; &lt;sup&gt;*&lt;/sup&gt;Also reported&lt;sup&gt;52&lt;/sup&gt;</td>
<td>25–37 (2M, 1F)</td>
<td>0</td>
<td>19–44 mo</td>
<td>Case series (part of 4 pt cohort)</td>
<td>IV</td>
<td>1. YGTSS 2 pts had modest reduction in tics (23%–34%) after initial CM-Pfc, Voa DBS but depression/OCD remained disabling 83% reduction in pt with simultaneous CM-Pfc, Voa + ALIC/NA</td>
<td>Yes (1 cut self with knife, 1 punched self in head)</td>
<td>1. None reported 2. ALIC/NA rescue leads were not very effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Servello et al., pGpi + ALIC/NA add-on</td>
<td>1</td>
<td>42 (F)</td>
<td>0</td>
<td>pGpi: 23 mo; Gpi + ALIC/NA (part of 36 pt cohort)</td>
<td>IV</td>
<td>1. YGTSS 14% improvement @ 23 mo with pGpi; 41% further improvement after ALIC/NA (49% total)</td>
<td>Not reported for this case</td>
<td>1. Required “rescue” ALIC/NA leads because of social impairment and poor QOL despite reduction in tics with Gpi DBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ackermans et al., 2006&lt;sup&gt;57&lt;/sup&gt;</td>
<td>pGpi + CM-Spv-Voi&lt;sup&gt; (<em>only Gpi activated</em>)&lt;/sup&gt;</td>
<td>1</td>
<td>27 (M)</td>
<td>0</td>
<td>1 yr</td>
<td>Case report (part of 2 pt series)</td>
<td>IV</td>
<td>1. Videotaped exam with tic frequency (tics/min) by 2 blinded raters; 93% reduction</td>
<td>No</td>
<td>No</td>
<td>1. Reduced energy level 2. Brief dystonic jerk each time turned ON</td>
<td></td>
</tr>
<tr>
<td>Welter et al., 2008&lt;sup&gt;71&lt;/sup&gt;</td>
<td>CM-Pf + Gpi (limbic)</td>
<td>3; &lt;sup&gt;*&lt;/sup&gt;1 previously reported&lt;sup&gt;43&lt;/sup&gt;</td>
<td>2F (36, 30); 1M (30)</td>
<td>0</td>
<td>20–60 mo</td>
<td>Controlled, double-blind, randomized crossover study + open long-term f/u</td>
<td>III</td>
<td>1. YGTSS (cross-over period) a) Gpi: 65%–96% improvement b) CM-Pf</td>
<td>None reported</td>
<td>Yes (eye mutilation, burning of skin)</td>
<td>No</td>
<td>1. Thalamic—decreased libido in 1 pt 2. Gpi—lathargy (3–4 d); nausea &amp; vertigo at higher settings (n = 2); anxiety (n = 1)</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Sample size</th>
<th>Age at DBS (years)</th>
<th>Subjects &lt; 25 yrs (ages)</th>
<th>Follow-up</th>
<th>Study Design</th>
<th>Level of Evidence</th>
<th>Tic Outcome Measures</th>
<th>Comorbidity</th>
<th>Outcome Measures</th>
<th>SIB With Immediate Risk of Bodily Harm (Yes/No)</th>
<th>Postoperative Lead Location Reported (AC-PC Coordinates)</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houeto et al., 2005</td>
<td>CM-Pf + GPi (limbic)</td>
<td>1</td>
<td>36 (F)</td>
<td>0</td>
<td>11 mo</td>
<td>Prospective double-blind randomized N = 1 crossover trial</td>
<td>III</td>
<td>1. YGTSS CM-Pf: 64% reduction GPi: 65% reduction “Sham” STIM: worse than baseline CM-Pf + GPi: 34% (60% reduction) 2. RVTRS CM-Pf: 77% reduction GPi: 54% reduction “Sham” STIM: 15% reduction CM-Pf + GPi: 77% reduction</td>
<td>1. MADRS 2. BAS (anxiety) 3. BIS (impulsivity) SUMMARY: CM-Pf: mood &amp; impulsivity improved: SIB resolved GPi: mood &amp; impulsivity worse than CM-Pf; SIB resolved SHAM: little change of depression/anxiety CM-Pf + GPi: SIB resolved</td>
<td>Yes (eye mutilation, burning of skin)</td>
<td>1. Weight loss (18 kg with CM-Pf, continued with GPi)—may have been related to withdrawal of neuroleptics 2. During SHAM stim: SIB, excoriations at cables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shields et al., 2008</td>
<td>ALIC/NA (“later revised to CM DBS”)</td>
<td>1</td>
<td>40 (F)</td>
<td>0</td>
<td>18 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 23% improvement</td>
<td>None reported</td>
<td>Yes (head-snapping tics, limb fractures, retinal detachment)</td>
<td>No</td>
<td>1. Lead extension fracture due to residual head-snapping tics after ALIC/NA DBS 2. Stimulation-induced altered mood and impulse control problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>48, 19 (2M)</td>
<td>1</td>
<td>(19)</td>
<td>Case series</td>
<td>IV</td>
<td>1. YGTSS</td>
<td>Yes</td>
<td></td>
<td>1. 48yoM:</td>
<td>(Continued)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target</td>
<td>Sample size</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
<td>Level of Evidence</td>
<td>Tic Outcome Measures</td>
<td>Comorbidities</td>
<td>Outcome Measures</td>
<td>SIB With Immediate Risk of Bodily Harm (Yes/No)</td>
<td>Postoperative Lead Location Reported (AC-PC Coordinates)</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Motlagh et al., 2013</td>
<td>1. Midline thalamic + pvGpi</td>
<td>1</td>
<td>26 (M)</td>
<td>0</td>
<td>30 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. Y-BOCS – 48yo had significant improvement (29-&gt;&gt;8); 19yo had no OCB 2. HDRS – both had worsening of depression 3. HARS – no change</td>
<td>Yes (2 of 2; slamming forearm against head, head-snapping tics + cervical injury; poking left eye, left cheek biting)</td>
<td>2nd target added due to continued head-snapping tics GPI lead extender malfunction due to head-snapping tics thalamic and GPI leads now OFF 2. 19yoM: ICU hospitalization with sedation for worsening tics 2mo after amGpi placement to prevent eye injury 3 separate DBS surgeries for 3 total bilateral targets due to refractory tics; currently has only R pvGpi lead on and no improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuhn et al., 2007</td>
<td>ALIC/NA</td>
<td>1</td>
<td>26 (M)</td>
<td>0</td>
<td>30 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS (52% improvement) 2. GAF—significantly improved (7-&gt;41)</td>
<td>None reported</td>
<td>Yes (head-snap ping tics, limb fracture, retinal detachments)</td>
<td>1. High stim requirements (2 IPG replacements in 30 mo) 2. Temporary deterioration in symptoms with battery depletion × 2 1. Stim-induced dysarthria, rhythmic jaw clenching 2. High-voltage stim in ventral contacts (near NA)—mild apathy and depression; dorsal contacts in body of capsule—agitated hypomania (hrs to days onset for mood effects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raherty et al., 2005</td>
<td>ALIC/NA</td>
<td>1</td>
<td>37 (F)</td>
<td>0</td>
<td>18 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 25% improvement 2. Patient tic logs 45% decrease in frequency and severity</td>
<td>None reported</td>
<td>Yes (head-snap ping tics, limb fracture, retinal detachments)</td>
<td>1. High stim requirements (2 IPG replacements in 30 mo) 2. Temporary deterioration in symptoms with battery depletion × 2 1. Stim-induced dysarthria, rhythmic jaw clenching 2. High-voltage stim in ventral contacts (near NA)—mild apathy and depression; dorsal contacts in body of capsule—agitated hypomania (hrs to days onset for mood effects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target</td>
<td>Sample size (n)</td>
<td>Age at DBS (years)</td>
<td>Subjects &lt; 25 yrs (ages)</td>
<td>Follow-up</td>
<td>Study Design</td>
<td>Level of Evidence</td>
<td>Tic Outcome Measures</td>
<td>Comorbidity Outcome Measures</td>
<td>SIB With Immediate Risk of Bodily Harm (Yes/No)</td>
<td>Postoperative Lead Location Reported (AC-PC Coordinates)</td>
<td>Adverse Events</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>----------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Zabek et al., 2008</td>
<td>ALIC/NA (unilateral R)</td>
<td>1 31 (M)</td>
<td>0 28 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. 15-min videotaped exams with tic counts 80% improvement</td>
<td>None reported</td>
<td>Yes (retinal detachment, blindness)</td>
<td>No 1. IPG malfunction at 9 months due to RUE motor tics --- sx deterioration — improvement after IPG replaced 3. IPG accidentally turned off several times—symptom worsening 4. Fractured lead extension requiring replacement—due to tics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuner et al., 2009</td>
<td>ALIC/NA</td>
<td>1 38 (M)</td>
<td>0 36 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 44% improvement 2. mRVTRS 58% improvements</td>
<td>1. Y-BOCS (56% reduction)</td>
<td>Yes (self-mutilation; breaking glass in hands)</td>
<td>No 1. Rapid IPG depletion—2 IPG replacements in 36 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burdick et al., 2010</td>
<td>ALIC/NA</td>
<td>1 33 (M)</td>
<td>0 30 mo</td>
<td>Case report</td>
<td>IV</td>
<td>1. YGTSS 15% worse in 1st 6 mo 2. mRVTRS Tics 20% worse @ 30 mo (&gt;6)</td>
<td>1. Y-BOCS (no significant improvement)</td>
<td>No Yes Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez-Torres et al., 2009</td>
<td>STN</td>
<td>1 38 (M)</td>
<td>0 1 yr</td>
<td>Case report</td>
<td>IV</td>
<td>1. RVTRS 97% improvement</td>
<td>1. UPDRS (pt had PD; 57% improvement)</td>
<td>No No Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Servello et al., 2009</td>
<td>ALIC/NA</td>
<td>1,*Previously reported (64) 47 (M)</td>
<td>0 10 mo</td>
<td>Case series (part of 4 pt cohort)</td>
<td>IV</td>
<td>1. YGTSS 79% improvement</td>
<td>1. Y-BOCS (54% improvement) 2. BDI (9% improvement—not significant) 3. STAI (19% improvement—no significant) 4. 10-pt VAS of social integration (no change)</td>
<td>No No No reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BAS, Brief Anxiety Scale; BIS, Barratt's Impulsivity Scale; CM-Pfc, Voa, centromedian nucleus-parafascicular, and ventro-oralis complex; CM-Spv-Voi, centromedian nucleus–substantia periventricularis-nucleus ventro-oralis internus complex; CM-PF, centromedian nucleus-parafascicular complex; Vop-Voa-Voi = nucleus ventro-oralis posterior, ventro-oralis anterior, and ventro-oralis internus complex; PI-DM-LM, parafascicular, dorsomedial nucleus, and lamella medialis; CM, centromedian nucleus region; GPi, globus pallidus internus; pvGPi, posteroverentral globus pallidus internus; amGPi, anteromedial globus pallidus internus; YGTSS, Yale Global Tic Severity Rating Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; BD1, Beck Depression Inventory; BD1-2, Beck Depression Inventory, 2nd Ed.; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; STAI, State-Trait Anxiety Inventory; AC-PC, anterior commissure–posterior commissure; mRVTRS, modified Rush Video-based Tic Rating Scale; RVTRS, Rush Video-based Tic Rating Scale; CAARS, Conners Adult ADHD Rating Scale; PDD-SQ, Pervasive Developmental Disorder-Self Questionnaire; TSSL, Tourette Syndrome Symptom List; YMRS, Young Mania Rating Scale; QOLAS = Quality of Life Assessment Schedule; SRSI-90-R, Self-report symptom inventory 90 items—revised; TSSR = Tic Symptom Self Report; BASC-2, Behavior Assessment System for Children—2nd Ed; TSOS, Tourette Syndrome Global Scale; PI-R, = Padua Inventory of obsessive compulsive disorder symptoms—Revised.
TABLE 2. Updates to 2006 TS DBS Guidelines

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2006 Guidelines</th>
<th>Revised Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>DSM-IV diagnosis of TS by expert clinician</td>
<td>DSM-V diagnosis of TS by expert clinician</td>
</tr>
<tr>
<td></td>
<td>&gt;25 yrs</td>
<td>1. Age is not a strict criterion</td>
</tr>
<tr>
<td>Tic severity</td>
<td>1. Severe tic disorder with functional impairment</td>
<td>1. Severe tic disorder with functional impairment</td>
</tr>
<tr>
<td></td>
<td>2. YGTSS &gt; 35/50</td>
<td>2. YGTSS &gt; 35/50</td>
</tr>
<tr>
<td>Neurropsychiatric comorbidities (ie, ADHD, OCB, depression, anxiety, etc.)</td>
<td>3. Document with standardized video assessment</td>
<td>3. Document with standardized video assessment</td>
</tr>
<tr>
<td></td>
<td>1. Tics should be the major symptom causing disability</td>
<td>1. Tics should be the major symptom causing disability</td>
</tr>
<tr>
<td></td>
<td>2. Comorbid conditions should be stably treated</td>
<td>2. Comorbid conditions should be stably treated</td>
</tr>
<tr>
<td></td>
<td>3. Comorbid conditions should be assessed using valid rating scales when available</td>
<td>3. Comorbid conditions should be assessed using valid rating scales when available</td>
</tr>
<tr>
<td>Failed conventional therapy*</td>
<td>1. Failed treatment trials from 3 pharmacological classes: a) alpha-adrenergic agonist, b) 2 dopamine agonists (typical &amp; atypical), c) benzodiazepine</td>
<td>1. Failed treatment trials from 3 pharmacological classes: a) alpha-adrenergic agonist, b) 2 dopamine agonists (typical &amp; atypical), c) a drug from at least one additional class (eg, clonazepam, tetrabenazine)</td>
</tr>
<tr>
<td></td>
<td>2. Evaluated for suitability of behavioral interventions for tics</td>
<td>2. A trial of CBIT should be offered</td>
</tr>
<tr>
<td>Comorbid medical disorders</td>
<td>Stable for 6 months before DBS</td>
<td>Stable for 6 months before DBS</td>
</tr>
<tr>
<td>Psychosocial factors*</td>
<td>1. Adequate social support without acute or subacute psychosocial stressors</td>
<td>1. Adequate social support without acute or subacute psychosocial stressors</td>
</tr>
<tr>
<td></td>
<td>2. Active involvement with psychological interventions when necessary</td>
<td>2. Active involvement with psychological interventions when necessary</td>
</tr>
<tr>
<td></td>
<td>3. Caregiver available to accompany patient for frequent follow-up</td>
<td>3. Caregiver available to accompany patient for frequent follow-up</td>
</tr>
<tr>
<td>Suicidal/homicidal ideation (SI/HI)*</td>
<td>Not specifically addressed</td>
<td>Documentation of no active SI/HI for 6 months</td>
</tr>
</tbody>
</table>

*Recommendations have changed since 2006.

TS, Tourette syndrome; DBS, deep brain stimulation; DSM, Diagnostic and Statistical Manual of Mental Disorders; YGTSS, Yale Global Tic Severity Scale; ADHD, attention deficit hyperactivity disorder; OCB, obsessive compulsive behaviors; CBIT, cognitive behavioral intervention therapy.

develop recommendations, and these were published in 2006. Subsequently, a collaborative international network of investigators was established, and in 2010 to 2011 the TSA commissioned an International Database/Registry of DBS outcomes and cases performed in patients with a diagnosis of TS. The purpose of this paper is to critically review the literature of all published cases of TS DBS and to provide updated opinions and recommendations for patient selection and assessment since 2006. Additionally, we aimed to encourage all clinicians and investigators who care for TS DBS patients to participate in the TSA DBS Database/Registry to collect more data and to enhance the understanding of surgical approaches and outcomes.

Since 1999, 48 TS DBS studies have been published, including approximately 120 patients from 23 centers in 13 countries. At least seven separate brain targets have been employed (Table 1). The most commonly used targets have been the medial thalamic region targets (eg, centromedian nucleus–parafascicular complex [CM-Pf]), with 70 reported cases. Thirty-one cases of pallidal TS DBS have been reported and have included both anteromedial globus pallidus internus (GPi; “limbic”) targets (n = 14) and posterovernal GPi targets (n = 16). One case report of globus pallidus externa (GPe) DBS has also been published. The anterior limb of the internal capsule/nucleus accumbens target in isolation has been used in six case reports, and one case of STN DBS has been reported in a patient who had both tics and Parkinson’s disease.

Eleven reported cases have employed more than one brain target (2 targets in 10 cases, and 1 case with 3 brain targets). In most of these cases, however, the additional target leads were added as “rescue” leads because of inadequate response to the initial TS DBS leads. Three cases reported were part of a prospective, double-blind, randomized crossover study comparing the CM-Pf and the anteromedial GPi targets. Although nearly all studies reported a beneficial effect on tics, most of these reports were uncontrolled cases (n = 100), and the results revealed wide variations in study methods and outcomes, thus limiting meaningful interpretation. Approximately one fifth of the papers did not report using a validated outcome or videotape analysis. Rating scales to capture TS comorbidities (eg, obsessive-compulsive behavior, anxiety) were used in fewer than one third of reported cases.
studies, and postoperative DBS lead locations were reported in only 10 of 50 studies.

Based on the levels of evidence classification scheme that has been used by the American Academy of Neurology, only four of these 48 studies met criteria for class III level of evidence (n = 19), whereas the others were class IV. Given the small number of patients and the use of multiple brain targets within the class III studies, these data would likely receive the lowest evidence rating (level U), indicating that the therapy remains unproven because of inadequate or conflicting data.

Since the last TSA guidelines were published in 2006, the field has gained important insight about safety and the potential for specific adverse effects of TS DBS. Thirty-three patients had TS DBS before the age of 25 years, including nine patients younger than 18. The risk of surgical complications and adverse events did not appear to be higher in these age groups when compared with patients older than 25 years. However, Servello et al., caution that three of the four cases who were implanted before the age of 20 years had less than satisfactory results after 3 to 6 months of follow-up (significant spontaneous waxing and waning of symptoms requiring frequent DBS programming).

Ackermans et al. reported substantial improve- in six patients on the Yale Global Tic Severity Scale (YGTSS) between the ON and OFF stimulation conditions (37%), and also improvement after 6 months of open-label therapy (49%) in a double-blind randomized cross-over trial of centromedian nucleus–substantia periventricularis–nucleus ventro-oralis internus (CM-Spv-Vo) DBS. Significant adverse effects were reported, including decreased energy levels as well as subjective gaze disturbances. One patient with comorbid depression, pervasive developmental disorder, compulsions, and severe self-injurious behavior had surgery under the condition of clinical urgency and had to be withdrawn from the trial because of severe postoperative complications with psychogenic paroxysmal hypertonia, disturbances of consciousness, and mutism. Somatoform disorder in this patient was only recognized retrospectively, and the patient eventually died of dehydration after refusing intravenous fluids.

Servello et al. has reported the most robust experience with TS DBS, and also published an important paper analyzing the rates of infectious and hardware-related complications for different DBS indications (eg, PD, TS, tremor, and dystonia). Servello’s group reported an increased risk of infectious complications in TS DBS (7 of 39 [18%] patients) compared with an overall infection rate for all DBS indications of 3.7% (10 of 272 patients). The TS DBS patients also may be at increased risk for hardware malfunction. Six cases of lead or lead extension fractures, or alternatively IPG malfunction, have been reported, four of which were attributed to residual head-snapping tics. These findings highlight the unique and potentially severe issues in the TS population. Whereas tics that are life threatening or carry significant risk of immediate bodily harm are observed in only 5.1% of all TS patients, nearly 50 TS DBS cases with significant SIB have been reported in the literature, with more than half of these cases involving a severe behavior or risk of severe bodily harm (eg, cervical myelopathy from head-snapping tics, bone fractures, retinal detachment).

Although few data are available to guide postoperative management of TS DBS patients, Servello et al. have the greatest experience with TS DBS to date. These authors have reported that TS DBS patients require more frequent visits for DBS adjustments (ie, in excess of monthly visits stipulated in their protocol) than for other DBS indications, and also TS DBS patients require substantial personal and family support. For this reason, a thorough evaluation of the patient’s adherence to recommendations, a clear assessment of the patient’s psychosocial situation inclusive of family dynamics, and the need for realistic patient and family expectations should be emphasized.

Given the dearth of double-blind controlled studies of TS DBS, the lack of consistent outcome measures related to TS comorbidities, and the lack of rigorous studies comparing brain targets, few data are available to guide target choice either in general or in specific patients.

Chronic continuous stimulation has been widely assumed to be the only effective approach to TS DBS. Recently, however, this notion has been challenged by Okun et al., who demonstrated the potential of non-continuous DBS paradigms in TS in a class III clinical trial planning study (n = 5) of safety and preliminary effectiveness. Additionally, these authors have suggested that responsive approaches may be possible, especially by using oscillations (eg, the gamma band) and other brain network oscillations associated with DBS efficacy.

Special Considerations Relevant to TS DBS and Guideline Updates

The official DSM V diagnostic criteria require the presence of tics for more than a year, with onset before the age of 18 years, and occurrence of both multiple motor and at least one phonic tic for a definitive diagnosis of TS. The variability (variability of tic types, as well as the waxing and waning of tic severity) in TS provides an extra level of complexity when
considering TS candidates for DBS therapy. Tics can be influenced by both environmental and psychological factors. Many TS patients can suppress tics partially or even completely for short periods, such as when being examined or when in public, but then release tics when returning to a more comfortable setting. The recognition of embellishment, psychogenic tics, factitious symptoms, personality disorders, and malingering all need to be considered in the preoperative workup, similar to the experience in epilepsy surgery with nonepileptic events.

A clinician with expertise and experience with TS patients should confirm the diagnosis by strict criteria and address all psychological comorbidities and non-motor features before consideration of DBS. Patient- or family-expressed psychological “urgency” should not heavily influence the clinician’s decision to proceed to an operation. All psychological and non-motor features should be stabilized before consideration for surgery. The evaluating team should be aware that the usual onset of TS occurs before the age of 10 years and has an average onset of 5.6 years. Tics typically follow a waxing and waning course, and they peak in severity in early adolescence. This peak is followed in most cases by a gradual reduction in tic severity in late adolescence and early adulthood. Longitudinal studies have reported either complete remission or alternatively mild tics in early adulthood for more than two thirds of TS patients. Clinicians selecting DBS candidates would likely benefit from a list of predictive factors that would facilitate identification of patients who will remain severely affected into adulthood. This information is not currently known. Recent research suggests that tic severity, premonitory urges, and a family history of TS may be childhood predictors of a worse health-related quality of life in adulthood.

Although TS rarely causes severe disability, and generally has a favorable prognosis, in a small subset of patients the symptoms cause severe disruption of interpersonal relationships, as well as impairments of social, psychological, and intellectual development. In extreme cases, TS may even become life threatening (eg, whiplash tics causing vertebral artery dissection or myelopathy). This severe form of the syndrome is associated with a higher rate of behavioral comorbidities (particularly OCD) and is more likely to be refractory to conservative medical management. Although malignant TS may affect only 5.1% of all TS patients, these cases will frequently come to the attention of TS DBS teams.

The appropriate age to perform TS DBS is unknown and has been widely debated. In 2006, the first TSA guidelines proposed a minimum age criterion of 25 years to ensure that individuals who might experience spontaneous tic remission would not be implanted with a surgical device. Since that time, compelling arguments have been made for consideration of surgical intervention at younger ages in certain cases of severe TS. The risk–benefit data for TS and for other DBS indications have shown that the actual DBS procedure is safe and well tolerated in children, particularly as demonstrated in those with dystonia. Because of increased evidence of a favorable risk–benefit ratio for DBS in children with dystonia and TS, the age guideline has been adjusted by most experts to recommend a multidisciplinary evaluation and discussion, without setting a firm age limit. Delaying surgery in younger incapacitated TS patients could potentially result in irreparable harm to social, psychological, and intellectual development, even if the symptoms eventually subside with age. Similarly, in rare cases of “malignant tics” that occur in younger individuals, the tics themselves (eg, whiplash tics) may carry greater risk for bodily harm, paralysis, or even death.

A feature of TS with implications for determining the efficacy of DBS is its frequent association with disabling psychiatric and behavioral comorbidities. The most common of these are ADHD and OCD. Comorbidities have a significant negative impact on the quality of life in TS and can be a larger source of impairment when compared with motor tics. Identification of comorbid psychiatric symptoms is critical for a DBS workup, because when left untreated, these symptoms may be the best predictors of a worse quality of life, with or without DBS therapy. Comorbid symptoms should be adequately treated before surgery, and patients should be informed that individuals who are deemed to be good candidates for DBS may experience a 30% to 50% or greater improvement in motor tics. However, based on all available published cases, how DBS will impact TS comorbidities remains unclear. Notably, comorbid OCD, ADHD, and mood issues have improved after DBS in some but not all cases.

Deep brain stimulation should be offered to TS patients only after evaluation by a multidisciplinary or interdisciplinary team. This team should include experts in TS and associated comorbidities (ie, neurologist, neurosurgeon, psychiatrist, neuropsychologist, DBS programmer [nurse or physician]). Centers performing DBS should have a high level of expertise with DBS therapy, especially given the complexities of the TS patient. Potential therapy candidates should be independently evaluated by each member of the team, and discussion of candidacy, risks, benefits, operative approach, and postoperative care should be pursued before a decision on candidacy is reached.

The ideal DBS candidate will have a DSM V diagnosis of TS and severe motor and vocal tics, which despite exhaustive medical and behavioral treatment trials result in significant impairment of self-esteem,
TABLE 3. Pre- and post-operative outcome measures recommended by the TSA*

Preoperative Information: Patient Assessment and Selection
- Age, sex, ethnicity
- Age of TS onset
- Age at diagnosis of TS
- Age at time of surgery
- Psychiatric comorbidities (OCB, ADHD, depression, anxiety, SIB, other)
- TS medications tried and stopped before DBS (medication name, dose, and duration of trial)
- TS medications at the time of DBS (including dose)
- Documentation of CBIT being offered or of the trial and outcome
- Standardized evaluation of tic type and severity (pre- and post-operatively)
  - Yale Global Tic Severity Score (YGTTSS)
  - Blinded video-based rating (e.g., Rush video scale rating of body regions involved, tic severity and frequency)
  - Premontory Urge for Tics Scale (PUTS)
  - Clinical Global Impression (CGI for TS)
- Standardized evaluation of comorbid symptoms with valid and reliable instruments when available (pre- and post-operatively)
  - Yale-Brown Obsessive Compulsive Scale (Y-BOCS)
  - Conners’ Adult ADHD Rating Scale (CAARS)
  - Depression: Beck Depression Inventory, 2nd Ed. (BDI-2), Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS)
  - Anxiety: Hamilton Anxiety Rating Scale (HARS), State-Trait Anxiety Inventory (STAI)
  - Mania: Young Mania Rating Scale (YMRS), K-SADS Mania Rating Scale (MRS)
  - CGI (for ADHD and OCD)
  - Suicide Assessment Scale (e.g., Columbia Suicide Severity Rating Scale)
  - Quality of Life Measurement (eg, Gilles-de-la-Tourette-Syndrome Quality-of-Life scale [GTS-QOL], Global Assessment of Functioning scale [GAF], SF-36)

Surgical Information: Targeting and Lead Location
- Brain target (e.g., CM-Pfc-Voa thalamus, Gpi, ALIC/NA, other)
- Procedure (unilateral, bilateral, simultaneous, staged)
- Lead models and IPG models used (e.g., Medtronic 3387/3389, ANS, Neuropace, primary cell, rechargeable, other)
- Lead location verification with postoperative MRI or CT (x-y-z coordinates of each contact in relation to the midcommissural point)

Postoperative Information: Programming, data and adverse events
- Stimulation parameters (active contacts, amplitude or current, frequency, pulse width, ± impedance) at each follow-up visit and time duration at that setting
- Frequency of programming adjustments (# to optimization, # per year)
- Stimulation-induced and general adverse effects
  - Psychiatric/cognitive (exacerbation of tics, mania, hypomania, cognitive decline, anxiety, OCB, depression, smile or laughter induction, impulsivity, psychosis, suicidal ideation/attempt, completed suicide, other)
  - General (paresthesias, muscle contractions, dyskinesias, bradykinesia, dystonia, dysarthria, stuttering, nausea or vertigo, lethargy, gait disorder, sexual side effects, weight loss/gain >10 pounds, death, other)
- Intraoperative or early surgical (1st post-op week) adverse events
  - Symptomatic/asymptomatic hemorrhage, ischemic stroke, seizure, post-op confusion, infection, air embolism, DVT, death, other)
- Delayed surgical adverse events (infection of intracranial lead, extracranial lead/lead extender infection, infection of IPG, lead dislodgment, lead fracture, lead revision, suboptimally positioned lead, lead removal, IPG removal, other)
- Timing of IPG replacement or need for recharging

(Continued)

Regular postoperative evaluations to include standardized rating scales of TS and co-morbidities
- YGTTSS
- Blinded video-based rating
- Y-BOCS
- Premontory Urge for Tics Scale (PUTS)
- Conners’ ADHD Scale
- Depression: BD-I-2, HDR-S or MADRS
- Anxiety: HARS, STAI
- Mania: YMRS, K-SADS, MRS
- CGI
- Suicide Assessment Scale (e.g., Columbia Suicide Severity Rating Scale)

* The exact measures are less important than the adherence to measurement of pre/post outcomes in each of the major domains (motor, non-motor, mood, quality of life).

TOURETTE SYNDROME DBS GUIDELINES

Inclusion and Exclusion Criteria

A DSM V diagnosis of TS should be made by an expert clinician who has experience in the evaluation and management of tic disorders (updated from DSM IV). Age should no longer be a strict criterion. Deep brain stimulation should be considered only when all standard medical and behavioral therapies have failed regardless of the patient’s age. Tourette syndrome DBS should rarely be an urgent indication, with the possible exception of impending paralysis from head-snarling tics or profound SIB. A local ethics committee or institutional review board should be consulted for consideration of cases involving persons younger than 18 years of age, as well as in cases with urgent indications, particularly those with lower YGTTSS scores or with shorter durations of symptoms.
TABLE 4. TS DBS Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DSM-V Diagnosis of TS by expert clinician</td>
<td>1. Active suicidal or homicidal ideation within 6 months</td>
</tr>
<tr>
<td>2. Age is not a strict criterion. Local ethics committee involvement for cases involving persons &lt; 18 years, and for cases considered “urgent” (eg, impending paralysis from head-snarling tics)</td>
<td>2. Active or recent substance abuse</td>
</tr>
<tr>
<td>3. Tic Severity: YGTSS &gt;35/50</td>
<td>3. Structural lesions on brain MRI</td>
</tr>
<tr>
<td>4. Tics are primary cause of disability</td>
<td>4. Medical, neurological, or psychiatric disorders that increase the risk of a failed procedure or interference with postoperative management</td>
</tr>
<tr>
<td>5. Tics are refractory to conservative therapy (failed trials of medications from 3 classes, CBIT offered)</td>
<td>5. Malingering, factitious disorder, or psychogenic tics</td>
</tr>
<tr>
<td>6. Co-morbid medical, neurological, and psychiatric disorders are treated and stable × 6 months</td>
<td></td>
</tr>
<tr>
<td>7. Psychosocial environment is stable</td>
<td></td>
</tr>
<tr>
<td>8. Demonstrated ability to adhere to recommended treatments</td>
<td></td>
</tr>
<tr>
<td>9. Neuropsychological profile indicates candidate can tolerate demands of surgery, postoperative follow-up, and possibility of poor outcome</td>
<td></td>
</tr>
</tbody>
</table>

The candidate should have a chronic and severe tic disorder with severe functional impairment. A standardized videotape assessment (eg, Rush Video-Based Tic Rating Scale\textsuperscript{94}) and a validated rating scale (eg, Yale Global Tic Severity Scale [YGTSS]\textsuperscript{95}) should be used to document tic severity. In most cases the TS patient should have a total YGTSS score greater than 35/50 documented over the course of a year.

Motor or vocal tics should be the primary symptom causing disability for a patient. Although most candidates are likely to have comorbid ADHD, OCD, depression, anxiety, or other non-motor symptoms, these symptoms should be adequately treated and stable for a minimum of 6 months and should not be the major source of functional impairment. In some patients, the commonly noted comorbidity of SIB, particularly severe SIB,\textsuperscript{96} may be inextricably intertwined with tics, and thus may be a primary contributor to disability. Patients with SIB or picking behavior should be warned preoperatively of an increased risk of infection or hardware-related complications.\textsuperscript{64}

At a minimum, documentation of unsuccessful treatment trials is needed from three pharmacological classes: (1) an alpha-adrenergic agonist, (2) two dopamine antagonists (including one typical and one atypical), and (3) a drug from at least one additional class (e.g., clonazepam, topiramate, or tetrabenazine). Tetrabenazine should be tried if accessible.\textsuperscript{97,98} In addition, CBIT delivered by a trained CBIT therapist should be offered,\textsuperscript{2,14} and the patient must have demonstrated his or her ability to adhere to recommended treatment plans before serious surgical consideration. Unfortunately, in many locations, including some centers experienced with TS, substantial issues of access, wait times, and lack of insurance reimbursement make therapies such as CBIT not always feasible, particularly in cases of malignant TS.

The neuropsychological profile must indicate that the candidate will be well suited to tolerate the surgical procedure, rigorous postoperative follow-up, and the possibility of both a negative or positive outcome.\textsuperscript{87} The potential for progressive cognitive impairment should be absent on this profile, or a follow-up profile should be performed to confirm findings and to also track progression.

Because of the substantial time commitment required for optimization of DBS therapy, as well as the significant impact that psychosocial factors can have on the disorder, any candidate for TS DBS must have adequate social support, and there should not be acute or subacute psychosocial stressors. A caregiver must be available to accompany the patient for visits and for frequent programming.

Similar to that proposed in the previous guidelines, there should be documentation of no suicidal ideation and no psychiatric hospitalization for 6 months before surgery. Depression and mood disorders must be stable and treated. Preferably suicidal tendency should be monitored preoperatively and postoperatively with a scale such as the Columbia Suicide Scale\textsuperscript{99} or another similar measure. Active or recent dependence on drugs or alcohol are contraindications for surgery. No structural lesions should be seen on magnetic resonance imaging that are deemed to present a significant risk by the neurosurgeon, nor medical, neurological, or cognitive disorders that would significantly increase the risk of a failed procedure, surgical complications, or interfere with postoperative management. A new criterion employed by most centers involved with TS DBS since 2006 is that an expert clinician should feel comfortable that malingering, factitious disorder, or psychogenic tics are not present.

Teams implanting TS patients should record preoperative and postoperative outcome measures, including age, disease duration, tic subtypes, motor, mood, behavior, quality of life, medications, postoperative lead locations, stimulation settings, and suicidal tendencies. Validated clinical rating scales of tics and TS comorbidities are critical. A full list of the measures recommended by the TSA and employed in in the International TSA DBS Database/Registry is provided in Table 3. The exact measures are less important than the adherence to measurement of preoperative
and postoperative outcomes in each of the major domains (motor, non-motor, mood, quality of life).

Discussion

The centers participating in the TSA International Database/Registry have employed several important practice pattern changes to the selection and assessment recommendations for the use of TS DBS. These changes were based on the expanded experience in the field since the 2006 guidelines. The changes and particularly the inclusion criteria (Table 4) reflect the growing experience with more than 120 cases reported worldwide. In particular, the relative safety of the procedure has been better established. Additionally, some TS cases may be appropriate for DBS before the previously recommended age of 25 years. Most centers now employ a multidisciplinary team approach for screening rather than an age limit. For patients younger than age
18, one should have additional institutional approval. Centers performing TS DBS should use preoperative and postoperative outcome measures, regardless of whether they adopt the TS DBS Database/Registry guidelines. All patients undergoing TS DBS should be aware that there is a reasonable chance for motor and vocal tic improvement, but that other co-morbidities in general respond less consistently to therapy. Clinicians should educate patients and families on the increased infection rate, and the potential for increased hardware-related issues. Figure 1 provides a diagram of the recommended evaluation before TS DBS.

The most appropriate brain target for an individual symptom profile remains unknown. The consensus of the centers implanting TS DBS includes the following: (1) all adverse events, whether major or minor, surgical or nonsurgical, related or unrelated to the therapy, should be recorded and reported; (2) detailed descriptions of all surgical and programming procedures should be recorded; and (3) preoperative and postoperative targeting should be reported, because where the optimal target regions are located, even within targets, remains unclear. Psychological issues should be screened preoperatively and monitored postoperatively. Finally, rigorous reporting of DBS failures and adverse events is needed.100 Databases and registries may be our best hope of advancing the field quickly, because most expert centers will do less than a handful of TS surgeries.

After an extensive review of the literature and consensus among implanters of DBS, we conclude that TS DBS, though still evolving, is a promising approach for a subset of medication-refractory and severely affected patients.

References


