PROGRESS IN SCIENTIFIC AND MEDICAL RESEARCH
Accomplishments, Advances and Impact
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A: EXECUTIVE SUMMARY

The Tourette Association of America was founded in 1972 with the aim of improving the lives of all people affected by Tourette and Tic Disorders. Today’s therapies help symptoms only partially. Therefore, the TAA invests in research which may lead to tomorrow’s breakthroughs in diagnosis and treatment. Towards this end, the TAA has and continues to develop, implement and oversee a wide range of programs to drive scientific and medical research into these conditions. These efforts have led to:

- Scientific discoveries in many areas of Tourette and Tic Disorders.
- Introduction of more treatment options and exploration of promising therapeutic strategies.
- Achievement of better patient outcomes through development and dissemination of best care guidelines and practices.
- Better understandings of Tic Disorders and their causes.
- Education and training programs that widen the network of care providers who understand and can better help patients with Tic Disorders and their families.
- A research grants & fellowships program which has led to breakthroughs, and has attracted substantial funding, experts and resources from elsewhere for research.
- The development of resources and infrastructures to support treatment discoveries, scientific breakthroughs, the scientists studying Tic Disorders, and significant funding from the federal government.
- Fostering of global research collaborations by building several consortia for coordinated research.
- The creation of partnerships to support the development and translation of research findings into patentable and marketable therapies.
- Establishment of global networks of thought leaders, and research strategies, to guide present and future advances in Tic Disorders.

In this report, we review the TAA-supported research accomplishments and advances over the past 45 years. We present emerging opportunities and highlight unmet needs which require further research and development. Above all, we highlight how the TAA’s research programs are central to the TAA’s mission of improving the lives of those impacted by Tourette and Tic Disorders.
TAA's research and medical programs over the past 45 years have led to the following 20 key discoveries, advances and developments in Tourette and Tic Disorders:

1. Discovery that Tic Disorders (Tourette Syndrome, Chronic Motor or Vocal Tic Disorders, Provisional Tic Disorder) have multiple causes which are complex interactions between genetics\textsuperscript{1-3}, environmental\textsuperscript{4} and/or other unknown factors.

2. Findings of gene, chromosomal loci and genetic variations (e.g. SLITRK, HDC, NRXN1 and CNTN6) that cause rare forms of TS, increase the risk of developing the disorder, and link TS with other conditions such as OCD\textsuperscript{5-10}.

3. In TS, MRI and other imaging studies show that various brain areas are structurally and functionally abnormal\textsuperscript{11-13}, and postmortem studies show that there are lower numbers of GABAergic neurons in the striatum\textsuperscript{14-16}, suggesting that these brain systems play a role in the development of tics.

4. Discovery that the limbic system, a region of the brain that underlies the expression of emotions, could also play a role in the occurrence of vocal tics and some behavioral features of TS\textsuperscript{17}.

5. Observations that alteration in circadian rhythms\textsuperscript{18-19} and brain excitability\textsuperscript{20-23} may contribute to differences in tic symptom onset, fluctuations and variations in treatment responses.

6. Creation of a ‘striatal disinhibition’ animal model that closely recapitulates tics, which can be used for exploring causes/mechanisms underlying Tic Disorders and testing treatments for these conditions\textsuperscript{24-25}.

7. Early clinical demonstration of effectiveness and later improvements in the use of many FDA and non-FDA-approved drugs, such as clonidine and aripiprazole (Abilify), that are now used routinely to treat TS\textsuperscript{26,27}.

8. Facilitated the first FDA-approval of a drug, Abilify (aripiprazole), for Tourette in over 30 years.

9. Discovery that a new class of drug, ecopipam, interacts with novel D1 dopaminergic targets in the brain and effectively reduces tics, with little adverse effects, in children and adults with TS\textsuperscript{28}.

10. Development of and clinical demonstration that Comprehensive Behavioral Intervention for Tics (CBIT), a medication-free behavior therapy, is as effective as drugs in some individuals with TS\textsuperscript{29,30}.

11. Showed that Deep Brain Stimulation (DBS) can effectively treat severe TS by stimulating specific areas in the brain, and have developed and published guidelines for its use in clinical practice\textsuperscript{31-33}.

12. Funding and supporting ongoing development of novel and promising treatment approaches for TS, such as medical cannabis\textsuperscript{34}, dental orthotic devices\textsuperscript{34,35} and home-based behavior therapies\textsuperscript{34}, some of which already have obtained US patent protection (US9486419B2) and Federal business grants (5R44MH096344-03, TicHelper.com), to support development and commercialization.

13. Launched a Centers of Excellence program\textsuperscript{36}, with 9 inaugural Centers at the nation’s leading healthcare/academic institutions, to develop, implement and maintain best practice guidelines to achieve the highest standard of care for people with Tourette and Tic Disorders.

14. Facilitated the consensus that Tic Disorders (TS, CMVT, PTD), represent a spectrum of neurodevelopmental conditions which are not rare\textsuperscript{37,38}. Tics occur in as many as 1 in 5 school-aged children\textsuperscript{19}. TS occurs in 1 in 166 (0.6%) school-aged children. The combined prevalence for all Tic Disorders is over 1% of school-aged children\textsuperscript{38,40}. 

B: KEY ACCOMPLISHMENTS AND BREAKTHROUGHS

$21$ Million
The amount the TAA has invested in 250 scientists since 1984 to develop new understanding of and treatment for Tourette Syndrome
B: KEY ACCOMPLISHMENTS AND BREAKTHROUGHS

15. Findings that OCD and ADHD occur frequently (up to 80%) in TS cases and may share genetic causes, but coprolalia is relatively infrequent (10%) in people with TS.\textsuperscript{41}

16. TAA programs, including a successful 13-year/$10 million partnership with Centers for Disease Control & Prevention, have developed and distributed an impressive library of authoritative information on TS, and have educated and trained over 350,000 individuals, including over 35,000 physicians and other care providers, on the disorder. This has led to increased awareness of Tic Disorders, development of a growing national referral network of 1,500 care providers\textsuperscript{42}, a more accurate and shorter time to diagnose Tic Disorders, and improved management of patients with better outcomes.

17. Hosted the 1st World Congress on Tourette Syndrome & Tic Disorders, which was the largest gathering of Tourette clinicians and scientists in the history of the disorder, with more than 430 attendees from 38 countries on 6 continents\textsuperscript{43}.

18. The TAA has invested over $21 million in small research grants and fellowships that have funded approximately 450 projects in 13 broad areas of research\textsuperscript{34}. These grants have attracted, retained, trained and supported over 400 established and early career researchers, located at 150 institutions in 16 countries across 5 continents, to drive progress in TS.

19. Between 2003-2013, every $1 of TAA research grant funding has led to nearly $10 in grant funding from institutions, such as the NIH, to support Tourette and related disorders research.

20. Establishment of a wide range of resources, (e.g. Research Grants and Projects Database\textsuperscript{34}, Brain Bank\textsuperscript{44}, Patient Recruitment Program\textsuperscript{45}, Gene Sample Collections\textsuperscript{46}), consortia (International Consortium on Genetics\textsuperscript{47,48}, Neuroimaging Consortium\textsuperscript{49}, International DBS Registry\textsuperscript{50} and Behavioral Sciences Consortium\textsuperscript{51}) and partnerships (e.g. NIH and CDC) to facilitate global collaboration on research into Tic and related disorders.

The aforementioned examples and other TAA-supported research accomplishments have provided: insights into the causes and brain changes underlying TS; increased medical, behavioral, surgical and other treatment options; improved access to skilled care providers, more accurate/timely diagnoses and better care outcomes; a better understanding of the occurrence of Tic Disorders; and research grants that have led to breakthroughs, as well as attracted many experts, partnerships/collaborations, large funding and other resources that are needed to facilitate research and discovery in TS.

TAA research programs have created new opportunities, such as the exploration of newly identified and novel treatment strategies, which are undergoing further research and development. The TAA’s efforts have also established global networks of thought leaders and research strategies to guide present and future advances in Tic Disorders.

Thus, TAA support for research over the past 45 years has had demonstrable impact and promises to continue driving the mission of making life better for all people affected by Tourette and Tic Disorders.

Since 2003, $1 of TAA research grant funding has helped investigators to obtain approximately $10 in grant funding for Tourette & related conditions from the National Institutes of Health (NIH)
C: SCIENTIFIC DISCOVERIES

1. Insights Into the Causes of Tourette and Tic Disorders

The TAA has provided funding, resources and expertise for research worldwide aimed at deciphering the causes of TS. These efforts have led to the following advances:

• It is now recognized that TS has multiple causes. Current concepts suggest a complex interaction between genetic risks, environmental and/or other factors.\(^1\)\(^-\)\(^4\).

• Family and twin studies show that TS is a hereditary disorder and, if a parent has TS, his/her children are 10 times more likely to develop the condition.

• TS seems to share some genetic background with other neurodevelopmental disorders, such as OCD, ADHD and autism spectrum disorders.

• Although research has not yet identified genes that cause or contribute to the majority of cases of Tic Disorders, our financial support, resources and/or expertise have helped to identify rare genetic causes (\textit{SLITRK1} and \textit{HDC}), chromosomal and variations of TS.\(^5\)\(^-\)\(^10\):

• The Tourette Association International Consortium for Genetics (TAAICG) and its collaborators have studied genetic material from over 2,400 individuals with TS and 4,100 people without TS. It was found that individuals with TS were up to 20 times more likely to have abnormalities (either duplicated or deleted genetic material) in two genes, \textit{NRXN1} and \textit{CNTN6}, that are involved in brain development. Together, abnormalities in these genes account for about 1% of TS cases. The TAAICG also found that individual duplications or deletions in other parts of the genome together account for another 0.5% of TS cases.

• TAA-funded research using patient registries in Europe indicate that pre and/or postnatal factors, such as parental psychological state (i.e. mood, anxiety, depression), may be implicated in the development of TS.

Thus, TAA support for research has provided a better scientific understanding of the causes of TS and related disorders, and has opened new avenues for exploration. For example, the discovery of HDC gene defects in TS suggests that brain histamine systems are involved in the development of tics and this has prompted the TAA to fund the clinical evaluation of histaminergic drugs as potential treatments for tics.

2. Brain Abnormalities Underlying TS

Brain abnormalities identified by neuroimaging studies

The TAA, through its research grants program and Neuroimaging Consortium (TANIC), has funded MRI and other imaging studies to determine the brain changes associated with the development of Tic Disorders.\(^11\)\(^-\)\(^13\). These studies are important as they can identify brain targets which may be exploited for developing therapies, such as DBS and neuropharmacological drugs. The TAA has funded:

• Anatomical studies which demonstrate a decrease in the volume of a certain brain area (caudate nucleus), thinning of the frontal cortex, and alterations in the corpus callosum of individuals with TS compared to those without the disorder.

• Studies that have found alterations in the activities of cortico-striatal-thalamic-cortical networks in TS.
C: SCIENTIFIC DISCOVERIES

These early studies point to structural and functional changes in the TS brain. The TANIC and other TAA-funded investigators will in future years continue to explore previously examined and other brain areas for alterations in TS using higher resolution equipment; greater and better characterized samples; and more comparable protocols across different sites. There also are many exciting avenues of study using neuroimaging techniques, which include:

- Research explaining how the brain differs in individuals with different Tic Disorders, and what brain changes are associated with the alterations in tic expression over time. Imaging studies also might lead to the development of tests to predict the onset and remission of tics.
- Work determining if different genetic subgroups correlate with different brain structures and functions.
- Studies elucidating the neuroimaging changes associated with the premonitory urge as this sensation precedes the development of tics in individuals with TS.
- Efforts to identify how behavioral therapies like CBIT, that are effective in reducing tics, alter brain networks.

Postmortem studies discover lower neuronal numbers in the striatum

Researchers at Yale University (New Haven, CT), funded by the TAA, studied brain samples from the TAA Brain Bank and found that the number of neurons in a region of the brain known as the striatum (part of the basal ganglia) was 50% lower in people with TS compared to those without the disorder. This reduction only affected a specific cell type, parvalbumin inhibitory and cholinergic interneurons, which normally act to suppress brain excitability and control movements. There also is loss of gene expression in the striatum in TS. Therefore, the loss of striatal neurons in TS could contribute to the generation of tics.

Researchers are now seeking to determine why there is a reduction of neurons in the striatum in TS, i.e. do they fail to be generated during brain development or do they subsequently degenerate? It is also important to determine if preventing the loss of neurons in the striatum, replacing them with stem cells or enhancing their functions using drugs might be effective treatment strategies for TS.

Brain areas involved in vocal tic generation

The TAA has funded neurophysiological studies to determine the brain networks that are involved in tic generation. McCairn and colleagues, who were funded by the TAA, showed that motor tics are a consequence of focal abnormalities in the sensorimotor networks of the brain, notably involving the basal ganglia. Conversely, vocal tics and many of the psychological abnormalities associated with TS appear to result from abnormalities in the limbic/emotional circuits. These researchers also have revealed an imbalance in a molecule called GABA, a neurotransmitter which inhibits brain activity, suggesting that discrete brain circuits may become too excitable and produce the involuntary behaviors associated with TS.

Why does tic expression fluctuate?

It is widely known that tic severity and frequency can fluctuate over both short and long periods of time. The biological basis of this is unknown and insights could help in the management of tics. Thus, the TAA is funding studies to determine the role of the circadian system in TS.
C: SCIENTIFIC DISCOVERIES

Investigators at the University of California-Los Angeles (Los Angeles, CA) are presently examining circadian rhythms in adults with Persistent Tic Disorders (PTDs) relative to healthy controls through lab-based measurement of evening salivary melatonin rise during dim light conditions (i.e. dim light melatonin onset), circadian phase preference (self-report), and 24-hour rest/activity rhythms (established from 10-day actigraphy and sleep diary monitoring)\textsuperscript{18-19}. This research is significant as case studies have shown that morning exposure to light therapy, known to advance circadian phase, is associated with modest to large tic reductions, potentially suggesting the presence of circadian abnormalities (i.e., circadian phase delay) in select individuals with PTDs. This phenomenon may contribute to tic symptom onset, course, and treatment response, and be linked to underlying PTD pathophysiology. Findings may enhance our understanding of the role of circadian rhythms in Tic Disorders and may provide new targets for future treatment development.

Brain excitability in TS and ADHD

Researchers at Cincinnati Children’s Hospital Medical Center (Cincinnati, OH), in collaboration with the Kennedy Krieger Institute (Baltimore, MD), are using a non-invasive technique called Transcranial Magnetic Stimulation (TMS) to evaluate levels of inhibitory signaling (which helps our brains “put on the brakes”) and neuroplasticity (a biological process which helps our brain cells make stronger connections for learning) in children with TS and ADHD\textsuperscript{20-23}. These brain-based measurements provide important insights about the developing brain and how it is affected by TS as well as by medication treatment. Currently, researchers are combining these studies with brain imaging and with techniques to understand sensory hypersensitivity problems in these children. The goal is to collect data that, in the future, could inform decisions about treatment and possibly provide completely new avenues for treatment of severe cases with brain stimulation.

3. Development of Animal Models of Tics

Animal models of human conditions are valuable research tools as they assist the exploration of causes and mechanisms of human diseases, as well as permit early testing of potential treatments before they are examined in people. The TAA has supported the development of various animal models of TS, including the ‘striatal disinhibition animal model’, which is generated by administering agents into a small area of the striatum, a brain area involved in the control of motor, associative and limbic information flow\textsuperscript{24-25}. The neuronal changes that stem from this focal loss of inhibition lead to the expression of motor tics in different animals, including non-human primates and rats, thus enabling the study of the mechanism underlying tic expression.

Recent studies used these models to address the key questions of ‘when’ and ‘where’ tics are expressed. The results of these studies revealed that the exact location of the disinhibition within the striatum determines the body part displaying the tics, while summation of the input from the cortex to this location determines the timing of individual tics. Currently, scientists are expanding this model to enable the study of common comorbidities of TS, such as ADHD, and to enable long term studies of the interaction between the animals’ behavior, state and medication with the rate and magnitude of their tic expression.

The striatal disinhibition animal model helped to unravel the underlying neural networks involved in tic generation, thus enabling future translational studies leading to the development of behavioral, pharmacological and medical-device based treatments for tic expression.
The TAA research grants and other funding mechanisms have supported studies exploring medical, behavioral, surgical and novel forms of treatments for TS and related conditions. These studies have now increased treatment options for TS and have opened new avenues for therapeutic explorations.

1. Existing and Emerging Drug Therapies

The TAA was instrumental in funding, recruiting subjects for and otherwise contributed to the demonstration of the benefits and potential side effects of many of the FDA- and non-FDA-approved drugs currently being used to treat TS (e.g. pimozide, haloperidol, aripiprazole, risperidone)\(^\text{26,27}\). Indeed, clonidine and guanfacine, which are now considered first-line pharmacological treatments for TS, were shown in early TAA-supported studies to be effective in reducing tic severity.

**Abilify**

Beginning in 2004, TAA-funded researchers began to examine aripiprazole (Abilify), for effectiveness and safety in individuals with TS. These studies found that aripiprazole was effective in reducing tics in adults and children and was safer compared to other drugs. These early TAA-supported investigations prompted Otsuka Pharmaceuticals to conduct a large scale clinical trial of aripiprazole for TS. The TAA drove recruitment for the Otsuka studies, which proved highly successful and led to the FDA approval of the drug for TS in 2014.

**Ecopipam**

The TAA has supported ($225,000) and driven patient recruitment for a clinical trial of a promising drug called ecopipam\(^\text{28}\). This drug is the first in its class to interact with D1 receptors and block dopamine which is thought to be overactive in TS and contribute to tic development. In the first open-label study, and in a subsequent Phase 2b double-blind, placebo-controlled, randomized trial, ecopipam was administered orally for several weeks to children or adults with TS. Patients were assessed using the Yale Global Tic Severity Score Total Scale (YGTSS-TS), which is a well-validated and standard measure of the clinical efficacy of drugs treating TS. Researchers found that ecopipam caused significant reductions in the YGTSS-TS at both two and four weeks after initiating treatment. Importantly, the drug was well tolerated with no clinically significant changes in standard clinical lab tests, ECG’s, heart problems, sedation and no increases in body weights, all of which often are seen with marketed drugs for TS. Ecopipam will now undergo additional evaluation for TS.

2. Behavior Therapies

In 2001, the TAA formed a Behavioral Sciences Consortium (BSC) comprising several clinicians, scientists and other experts. The group was asked to work collaboratively to develop nonpharmacological treatments for TS. The TAA invested approximately $300,000 to support several planning meetings and small pilot studies, which resulted in the conceptualization of a therapy called Comprehensive Behavioral Intervention for Tics (CBIT)\(^\text{29,30}\). The TAA BSC subsequently obtained over $8 million from NIMH to support further research and development of CBIT.
Several years ago, the TAA BSC conducted randomized, controlled, clinical trials to evaluate the effectiveness of several sessions of CBIT given over 10 weeks compared to supportive therapy/education in 126 children (ages 9-17) or 122 adults (ages 16-69) with Tic Disorders. It was found that CBIT significantly reduced tic severity and there were little or no significant adverse effects. These benefits were similar to those seen with medications used in the treatment of tics in TS.

CBIT has now become a first-line of treatment for many individuals with Tic Disorders. The TAA, through its Behavior Therapy Institute (BTI) and a partnership with the CDC, has been aggressively educating and training thousands of care providers across the US on CBIT. As a result, the TAA has a growing referral database of skilled CBIT practitioners which is available to patients.

TAA-funded research and other researchers now are working to optimize the CBIT protocol to improve patient compliance and adoption by diverse professionals (e.g. occupational therapists). They also are seeking to develop novel methods of delivery of CBIT using telemedicine strategies (www.tichelper.com) and home-based, self-help, approaches to increase patient access, especially for underserved regions of the US.

### 3. Surgical Treatment – Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a promising neurosurgical treatment for TS that may improve disabling tics in severe, therapy resistant forms of TS. The TAA has funded research through our grants program and via the international DBS Registry to develop and later seek FDA-approval for this treatment strategy. This project so far has accomplished the following:

- Research has demonstrated that deep brain stimulation of the thalamic centromedian nucleus is effective in reducing tics in individuals with severe TS.
- New guidelines have been published to guide physicians and neurosurgeons on the use of DBS in treating TS.
- Investigators have been analyzing medical, surgical and adverse event data in the Registry collected from 163 TS DBS patients drawn from 31 institutions across 9 countries. These analyses have shown that, of the total cohort, 72% were male with an average age at surgery of 29.5 years, though the youngest patient in the cohort was 13. OCD symptoms were present in 60% of patients, however only 20% had self-injurious behavior.
- The pooled one-year outcomes revealed a significant improvement in tic severity. The one year follow-up results from this multi-national DBS Registry and database revealed clinical benefits in many patients, however, there were more side-effects than expected.

The Registry data will aid practitioners, educate potential TS DBS candidates and provide useful information to drive improvement of the procedure.

### 4. Novel Treatment Research

The TAA has a history of funding investigations into novel treatment strategies which may become proven therapies for tics and other symptoms of Tic Disorders. Thus, because of credible or promising preliminary evidence, the TAA is currently funding clinical or scientific studies in several areas. These studies are ongoing and, when completed, findings will be published in peer-reviewed journals and
D: TREATMENT ADVANCES

made available to the public. Importantly, some of these TAA-funded studies have already led to the filing and approval of patents describing novel treatment approaches for TS.

Medical Cannabis

Medical cannabis has been reported to reduce symptoms in TS and other neurological conditions. However, previous clinical trials have lacked sufficient sample size to provide conclusive results. Thus, the TAA is currently funding several grants to evaluate various formulations of medical cannabis under IRB-approved, regulated protocols.

The TAA is also funding research studies to develop agents that are similar to the active components of medical cannabis (i.e. cannabidiols, cannabinois and tetrahydrocannabinols), to determine how they interact with the cannabinoid system/receptors, and evaluate their potential for reducing symptoms of Tic Disorders. Indeed, TAA-funded research examining the therapeutic potential of targeting the endocannabinoid system CB2 receptors, using ligands, has demonstrated positive laboratory results and US patent protection (US9486419B2).

Thus, medical cannabis and its associated brain systems represent promising treatment strategies for TS and will undergo further laboratory and clinical exploration in the future.

Dental orthotic devices

There have been reports in the public domain that removable dental orthotic devices can reduce tics in individuals with TS. Thus, in 2011, the TAA brought together several dentists and clinical experts in TS to collaborate on the evaluation of this potential treatment approach. This led to the development of a clinical trial protocol which underwent review and approval by the TAA’s Scientific Advisory Board. The project was funded in 2012 by the TAA with a grant of $150K.

The study, entitled “Proof of Concept Study of an Oral Orthotic to Reduce Tic Severity in Chronic Tic Disorder and Tourette Syndrome”, is being led by Drs. John Walkup and Shannon Bennett at the Weill Cornell Medical College in New York. It is a randomized, controlled, feasibility trial of an active vs sham oral orthotic to reduce tic severity in 24 children and adolescents ages 7-25 years with TS or Tic Disorders. The study is underway and is expected to be completed December 2017.

This is the first TAA-supported clinical trial of a dental orthotic device. If the data show tic reduction, this will form the basis of a larger, more comprehensive trial to provide a better understanding of the effectiveness and safety of dental orthotic devices as a treatment for Tic Disorders.

Other treatment approaches undergoing evaluation

- Biofeedback using imagined finger movement for tic suppression.
- Transdiagnostic treatment aimed at specific symptoms rather than diagnoses.
- Transcranial Magnetic Stimulation (TMS).
E. ESTABLISHING BEST CARE GUIDELINES AND PRACTICES: Centers of Excellence Program

The TAA Centers of Excellence (CofE) program aims to improve the quality of life of people with Tourette Syndrome and other Tic Disorders by promoting the highest levels of care, research, education & training, and advocacy and awareness for these conditions.

CofE Program Blueprint And Criteria

In 2013, the TAA brought together leading medical and scientific experts in Tourette and related conditions to develop a CofE blueprint to reflect and guide the needs of the Tic Disorders community. Immediately thereafter, an open invitation was issued nationally to receive applications for the designation from prospective centers. In 2014, after an extensive assessment process led by an independent Advisory and Review Committee (ARC), 9 centers comprising premier medical and academic institutions across the US were found to meet the blueprint criteria and were designated TAA CofEs.

As mandated by the blueprint, which is available in full on our website and summarized here, all Centers are required to provide:

Expert and Coordinated Care: TAA CofEs provide timely and accurate evaluations of TS and related conditions. Thus, patients may receive coordinated care using evidence-based treatment and management approaches from multidisciplinary teams of care providers. Clinical services offered include:

- Child and Adult Neurology and Psychiatry Specialties
- Allied Health Care Providers
- Evaluations, Diagnoses and Advice
- Medical Treatments
- Behavioral Therapies (e.g. CBIT/CBT)

- Counseling and Psychological Services
- Occupational Therapy
- Deep Brain Stimulation (DBS)
- Botulinum Toxin Therapy
Research: Centers conduct or collaborate on scientific and clinical research studies within their own institutions or elsewhere. These investigations aim to provide a better understanding of TS/Tic Disorders, their impact, and to advance the development of more effective and safe treatments.

Education and Training: Centers provide training and education to healthcare professionals and researchers on Tourette Syndrome, Tic and related disorders. These centers also help educate patients, families and the general public on these conditions.

Advocacy and Awareness: TAA CofEs work with the national Association and its local chapters and support groups to improve awareness and advocate for TS in their local communities and nationally.

TAA CofE Work and Impact

The TAA CofE program is in its infancy and requires further development before its mission is fully attained. At present and annually, TAA CofEs:

- Collectively publish approximately 80 papers on their research covering a broad range of clinical and scientific studies into Tic and related disorders.
- Host or participate in approximately 150 events (e.g. walks, support group meetings, presentations, etc.) annually within their communities and nationally.

Each CofE cares for a total of 450 patients, 90 of which are newly diagnosed cases, on average per year. However, the number and types of patients seen by the various TAA CofEs vary significantly due to geography.

Together train in the region of 210 residents & fellows in Tic Disorders and other areas of neurology, psychiatry, pediatrics, etc.
E. ESTABLISHING BEST CARE GUIDELINES AND PRACTICES:
Centers of Excellence Program

TAA CofE Locations

1. BAYLOR COLLEGE OF MEDICINE, HOUSTON, TX
   Director: Joseph Jankovic, M.D.
   Co-Director: Suzanne Mouton-Odum, Ph.D.
   Tel: (713) 798-2273

2. CHILDREN’S MERCY HOSPITAL, KANSAS CITY, MO
   Director: Keith Coffman, M.D.
   Co-Director: James Batterson, M.D.
   Tel: (816) 346-1384

3. JOHNS HOPKINS HOSPITAL, BALTIMORE, MD
   Director: Harvey Singer, M.D.
   Co-Director: Marcos Grados, M.D.
   Tel: (410) 955-4259

4. MASSACHUSETTS: GENERAL HOSPITAL, BOSTON, MA
   Director: Jeremiah Scharf, M.D., Ph.D.
   Co-Director: Sabine Wilhelm, Ph.D.
   Tel: (617) 726-5532

5. NEW YORK STATE CONSORTIUM:
   Weill Cornell Medical College, New York, NY
   Director: John Walkup, M.D.
   Co-Director: Shannon Bennett, Ph.D.
   Tel: (212) 821-0789

   Northwell Health, Manhasset, NY
   Director: Cathy Budman, M.D.
   Co-Director: Jane Zwilling, Psy.D.
   Tel: (516) 562-3051

   University of Rochester Medical Center, Rochester, NY
   Director: Jonathan Mink, M.D., Ph.D.
   Co-Director: Heather Adams, Ph.D.
   Tel: (585) 275-2808

   Icahn School of Medicine at Mount Sinai, New York, NY
   Director: Barbara Coffey, M.D.
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TAA Advisory and Review Committee
(See section K)
The TAA has driven advances in understanding of Tourette and Tic Disorders for decades. In 2014, the TAA brought together over 20 thought leaders and experts in TS to review the state of the field and develop a consensus to clarify several misunderstandings on the occurrence of TS and related disorders.

**Spectrum Disorders**

Tourette Syndrome (TS) belongs to a spectrum of neurodevelopmental conditions referred to as Tic Disorders. This group also includes Chronic Motor or Vocal Tic Disorders (CMVTD) and Provisional Tic Disorders (PTD). These conditions share many similarities, but differ on the basis that TS requires the presence of both motor and vocal tics for at least 1 year; while the presence of either motor or vocal tics (not both) for more than 1 year is required for a diagnosis of CMVTD. Individuals with tics present for less than 1 year are given a diagnosis of PTD. Importantly, the spectrum of Tic Disorders is not linear with respect to severity, as each disorder can be more or less severe than the others in the group.
Tic Disorders Are Not Rare

TS and other Tic Disorders are not rare. Tics occur in as many as 1 in 5 school-aged children. Some occurrences may be transient, while others will persist into adolescence and adulthood. The combined prevalence of TS and other Tic Disorders is estimated to be over 10 cases per 1,000 (1%, 1:100), suggesting that over 1/2 million children have a Tic Disorder in the US. The best estimate for the prevalence of TS is 6 cases per 1,000 (0.6%, 1:166) children, which means that approximately 300,000 children have the condition in the US (based on 2010 Census data). There are currently no reliable prevalence estimates of TS and other Tic Disorders in adults, but they are expected to be substantially less than in children as tics often decline with aging.

Comorbidities and Coprolalia

Many associated conditions, the most common being OCD and ADHD, occur in up to 80% of individuals with TS and Tic Disorders. Coprolalia is relatively rare in individuals with TS (1 in 10), is not required for diagnosis, and does not persist in many cases.

Impact

Tics and associated symptoms in Tic Disorders may range from mild/inconsequential to moderate to severe and, in some cases, can be debilitating with a profoundly negative impact on quality of life. Indeed, many individuals with Tic Disorders do not need or seek treatment, while others require multiple and repeated therapeutic interventions to manage tics and other symptoms of co-occurring conditions.

Treatment is generally considered when tics are painful, distressing, or interfere with social, academic and professional life. When needed, treatment strategies for all Tic Disorders are the same, and may include medication and/or behavioral therapies (e.g. CBIT, CBT). Surgical treatments (e.g. DBS) continue to be developed and should be considered only for the most severe, drug/behavior therapy-refractory cases of Tic Disorders.
G: EDUCATION AND TRAINING

Since TS was discovered, there has been a long history of misconceptions of the condition among the lay public and poor understandings of the disorder among health care providers. This has led to stigma, bullying, erroneous or delayed diagnosis, and inadequate treatment outcomes. Thus, the TAA research and medical programs, in collaboration with our external partners, have led the way in educating and training all sectors of the TS community. These efforts have achieved the following:

1. Behavior Therapy Institute

Comprehensive Behavioral Intervention for Tics (CBIT), which is a combination of different behavioral therapies, was developed under the TAA’s leadership and has proven to be as effective as medication in reducing tics. To assure the availability of highly skilled CBIT providers, the TAA launched its Tourette Syndrome Behavior Therapy Institute (TS-BTI) in 2011 to increase the training of healthcare professionals on CBIT, thereby accelerating dissemination of this therapy.

The TS-BTI is held over 2 days and followed by a post-training consultation phase. At this time, approximately 362 professionals have been trained, with nearly half (175) who have completed the certification process.

BTIs have been held in several states (Arizona, California, Florida, Illinois, Kentucky, Louisiana, Maryland, Massachusetts, Missouri, New York, Utah, Virginia, and Washington, DC), and at several locations in Canada (Mississauga, Niagara Falls and Vancouver). These events have been attended by care providers from all over the world (Argentina, Australia, Canada, Germany, Taiwan, Spain, and Puerto Rico).

The TAA continues to develop a behavior therapy referral list of qualified care providers, which is currently available to anyone seeking treatment information for TS.
G: EDUCATION AND TRAINING

2. Tourette Health and Education Program (TAA-CDC Partnership)

Since 2004, the TAA has received over $10 million in grants from the US Centers for Disease Control and Prevention (CDC) supporting the Tourette Health and Education Program (THEP). This funding was made possible by Title 23 of the Children’s Health Act, signed by Congress in September of 2000, and authorizes a Public Health Education and Research Program on Tourette Syndrome.

The TAA's partnership with the CDC has led to the development of authoritative materials and delivery of over 1,000 free educational opportunities (in-person and online) to nearly 350,000 care providers, school personnel, families, individuals, and members of the general public. Program topic areas include diagnoses, management, impact of co-occurring conditions, and living with TS. Among its many accomplishments, THEP has played an important role in efforts to increase interest in and knowledge of CBIT as an effective treatment among practitioners. THEP also drives the identification and addition of care providers to the TAA national referrals database.

THEP continues to expand its reach and impact by streaming program content online, utilizing social media, and developing a robust series of resources to better equip the community with the tools necessary to navigate the often complex TS landscape.

3. 1st World Congress on Tourette Syndrome & Tic Disorders

The TAA, in collaboration with its international partners, The European Society for the Study of Tourette Syndrome (ESSTS) and Tourettes Action UK, joined forces to host the 1st World Congress on Tourette Syndrome and Tic Disorders, held in London, June 24 through 26, 2015. This was the largest gathering of experts and presentation of findings in the history of these disorders.

Research scientists, physicians, neurosurgeons, psychologists, social workers, residents, fellows, students and others from 38 countries and six continents gathered for the international meeting. Presentations and discussion took place in all areas, including drug development, genetics, comorbid conditions, surgical therapies and behavioral treatments for children and adults living with TS and Tic Disorders. Experts presented 185 scientific abstracts and 161 posters with significant discoveries and developments which have the potential to change our understanding of these conditions. A comprehensive library of research abstracts from the Congress is available for download online. Importantly, the Congress established a new global workforce and international collaboration focused on Tourette and Tic Disorders.

The 1st World Congress on Tourette and Tic Disorders set the precedent for a broad exchange of ideas, strategies and partnerships for research and discovery into Tourette and Tic Disorders. The impact of the Congress has already accelerated progress and will continue to facilitate advances in TS and Tic Disorders towards the 2nd World Congress and beyond.

The 1st World Congress was supported by a grant ($10,000) from NIH/NINDS, and by various industry (Neurocrine Biosciences and Psyadon Pharmaceuticals) and individual donors.

To download abstracts from the World Congress, visit tourette.org/Abstracts
G: EDUCATION AND TRAINING

4. Authoritative Publications

The TAA has supported the development, writing and publication of a wide range of scientific and medical information on TS and related disorders. These have been disseminated widely and serve to inform and guide both the professional and lay individuals interested in Tourette.

The TAA has supported research leading to the publication of hundreds of original scientific papers and reviews in international, peer-reviewed journals. These include some of the world’s highest ranking journals, such as JAMA, Neuron, Proceedings of the National Academy of Sciences, Nature, etc.

Our organization has commissioned, written and/or funded the authorship of many chapters and books on all aspects of Tourette which have and will continue to serve as essential references on Tourette.

The TAA has developed a wide range of audio-visual materials that are used regularly to train professionals on the diagnosis and management of Tourette Syndrome. These publications, many of which are seminal and highly cited, places the TAA as arguably the most authoritative source of information on Tourette and Tic Disorders in the world.

Recent TAA-Supported Publications

a. A Guide To Diagnosis And Treatment of Tourette Syndrome.
b. A Family’s Guide To Tourette. Edited by John T. Walkup, M.D., Jonathan W. Mink, M.D., Ph.D., Kevin St.P. McNaught, Ph.D.
c. Tourette Syndrome: 10 Secrets To A Happier Life. Edited by Michael S. Okun, M.D.
e. Navigating Tourette Syndrome: A Patient’s Guide To Diagnosis, Treatment And Support.
f. 1st World Congress On Tourette & Tic Disorders: Frontiers Abstract Book. Edited by Marc Scullin, MA
The TAA research grants and fellowships program was established in 1984 with the aim of providing funding to: (1) Explore novel concepts in Tic and related disorders. (2) Generate preliminary data that can be used as the basis of grant applications to obtain larger funding research from NIH and other federal and non-federal entities. (3) Attract experts from other disciplines and retain promising members in the TS field. This program has been successful in all 3 aforementioned areas.

1. Over the past 30 years, the TAA invested over $21 million which has funded 442 grants and fellowships to 400 Investigators in 13 research areas. The program has also attained global reach, with awards going to 150 prestigious institutions from 16 countries on 5 different continents.

2. Supported the discoveries outlined elsewhere in this document, including the development of CBIT, discovery of rare genetic causes and risk genes for TS, discovery of alterations in the basal ganglia in TS, the development of an animal model of tics, and the exploration of novel treatments such as dental orthotic devices and medical cannabis.

3. Between 2003 and 2016, the TAA funded 134 investigators for a total of approximately $15 million. Forty nine (approximately 40%) of those investigators funded during this period have gone on to receive NIH funding for 127 grants, worth approximately $135 million. Thus, every $1 the TAA has invested in grants has resulted in approximately $10 of funding from the NIH.

4. Helped Suzanne Mouton-Odum, Ph.D. (PsycTech, Ltd), Douglas Woods, Ph.D. (Marquette University, Milwaukee, WI) and Mike Himle, Ph.D. (University of Utah, Utah), to obtain a Federal small business grant (5R44MH096344-03, $420,490) to commercialize behavior therapies (TicHelper.com).

5. Led to discoveries of novel endocannabinoid system/CB2 receptor-based treatment strategies for TS which successfully obtained US patent protection (i.e. US9486419B2).
6. Launched the careers of many prominent investigators who have become experts in the TS field, including Jeremiah Scharf M.D., Ph.D. (Massachusetts General Hospital, Boston, MA), co-chair of the TAA International Consortium for Genomics; and Flora Vaccarino M.D. (Yale University School of Medicine, New Haven, CT), a member of the TAA Center of Excellence at Yale Child Study Center:

a. Dr. Scharf has received approximately $200,000 in grants from the TAA over the course of his career. More impressive, Dr. Scharf has received approximately $4 million dollars in funding from the NIH since his first award from the TAA in 2005. Every $1 that the TAA has invested in Dr. Jeremiah Scharf since 2005 has resulted in $20 of funding from the NIH.

b. Dr. Vaccarino has received approximately $400,000 in grants from the TAA over the course of her career. In the time since her first TAA award in 2004, Dr. Vaccarino has been granted approximately $27 million dollars in funding from the NIH. Every $1 that the TAA has invested in Dr. Flora Vaccarino since 2004 has resulted in approximately $75 of funding from the NIH.

This astounding return on TAA investment for Drs. Scharf, Vaccarino and many other investigators demonstrates not only the power of the grants and fellowships program to launch promising careers, but its overall value to the Tourette community. Both Drs. Scharf and Vaccarino are active members of the TAA Centers of Excellence team at their respective institutions and Dr. Scharf serves on the TAA Scientific Advisory Board.
I: DEVELOPMENT OF RESEARCH RESOURCES AND INFRASTRUCTURES

1. Research Grants and Projects Database
Since 1984, the TAA has awarded 442 research grants and fellowships to support scientific, clinical and other research into Tic and related disorders34. These awards have supported over 400 investigators, working at 150 institutions in 16 countries, on 5 different continents. The projects cover 13 areas of research: neurophysiology and neuroanatomy, genetics, cell and molecular biology, drug trial and pharmacology, neuroimaging, animal model, behavior therapy, immunology, epidemiology, neuropathology, clinical phenotype and behavior, alternative therapy, and deep brain stimulation.

2. Brain Donor and Banking Program
The TAA brain donor and banking program was established in 1984 and continues to provide researchers with samples needed to determine the brain changes that underlie the development of Tourette and related disorders34. Samples are collected, maintained and distributed through partnerships with Brain Bank Director, Dr. Rosalinda Roberts, at the University of Alabama and the Harvard Brain Tissue Resources Center at the McLean Hospital in Belmont, MA. These samples have been used by researchers to discover neuronal loss and gene expression changes in the striatum in individuals with TS. The TAA Brain Donor and Banking Program remains a valuable resource and is available for ongoing and future studies in Tic Disorders.

3. Patient Recruitment Program
Over the years, the TAA’s patient recruitment program has been an important component of several successful clinical trials45. Through our extensive chapter network and vast partnerships with the most prestigious academic and medical institutions around the country, the TAA has been able to drive recruitment for several breakthrough medication trials. Most notably, the TAA partnered with Otsuka and was an integral part in recruiting participants for studies that led to the 2014 FDA approval of aripiprazole (Abilify) for treatment of TS, which marked the first significant medication development for TS in decades.

The TAA is working with other companies, including Psyadon Pharmaceuticals (ecopipam), Neurocrine Biosciences (valbenazine) and Abide Therapeutics (ABX-1431), to bring new medications for Tic Disorders to the market. Through endeavors like the Patient Recruitment Program, the TAA remains committed to its role as an authority on evidence-based treatments for TS and other Tic Disorders.

4. Referral Database and Public Inquiries
The TAA has built a reputation for providing the professional and lay communities with authoritative information on TS and Tic Disorders, as well as providing referrals for people seeking treatment.

- The TAA has developed and maintains a database42 of nearly 1,500 care providers, including MDs, PhDs, OTs, RNs, physicians, surgeons, allied professionals, and others. The database is continually updated and is available through our website at all times for individuals searching for TS care providers in their geographic locations across the US. To locate a provider in your area, visit www.tourette.org/find-a-doctor/.

- Annually, of the nearly 1000 inquiries that the TAA receives by phone and electronic communication, 60% relate to medical and scientific matters.

### TAA MAP Referral Database Provider Specialty Areas

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<th>Specialty Area</th>
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</table>

1,899 Total Providers
The TAA recognizes that, while competition in research can be advantageous, it is equally important to facilitate collaborations where sharing expertise and resources are required to drive discovery. Thus, we have established and manage several consortia comprised of experts in the US and overseas.

1. **TAA International Consortium for Genomics**

The TAAICG was founded in 1986 by TS genetic researchers in the United States, the Netherlands, and Canada, and was brought together by the TAA to exchange ideas and share preliminary data with the goal of identifying TS susceptibility genes. To date, the TAAICG has recruited and enrolled 4,020 independent TS cases and 3,500 family members for genetic studies, and has established collaborations with all other major Tourette Syndrome consortia in the US and Europe, including TIC Genetics, TSGeneSEE and EMTICS.

**Funding**

The TAA provided initial seed funding for the TAAICG that was used to attract a $15 million U01 cooperative grant and subsequent $1.7 million ARRA grant, both from NINDS, for the consortium’s work.

**Membership**

The TAAICG has 29 members in the US and overseas, and is currently led by Carol Mathews, M.D. (University of Florida, Gainesville, FL) and Jeremiah Scharf, M.D., Ph.D. (Massachusetts General Hospital, Boston, MA).

**Goals**

The team is working to understand the underlying genetic causes of TS through multiple approaches, including linkage, genome wide association studies (GWAS), copy number variants (CNVs), exome sequencing, and endophenotypes studies. They have developed clinical assessment tools that are now the standard for genetic studies in all of the TS consortia, as well as web-based assessment tools. Consortium members have investigated the genetic relationships between TS, OCD, ADHD and major psychiatric disorders, and in collaboration with others, have examined the relationships between TS and other major neurological disorders.
J: FOSTERING COLLABORATIONS BY BUILDING CONSORTIA

Research

Early studies focused on parametric linkage analyses in large, multi-generational TS families under the assumption that TS was a monogenic disorder. However, as evidence mounted to indicate the presence of non-Mendelian inheritance, the TAAICG expanded to 11 clinical sites in the USA, Canada, Germany, the UK, and the Netherlands to collect TS affected sibling pairs for non-parametric analyses using a standardized phenotypic assessment for TS, OCD, and ADHD, still used today by the three international TS consortia.

The TAAICG was awarded NIH funding in 2000 to collect additional small nuclear families and completed a high-density linkage study of all existing affected sibpairs and multi-generational families (TAAICG, 2007). These analyses of over 2,000 individuals identified a genome-wide significant non-parametric linkage signal on chromosome 2p, though subsequent analyses have demonstrated significant heterogeneity across this locus, consistent with the presence of multiple distinct signals within the linkage region. With the advent of the GWAS era, the TAAICG changed its collection goals to focus on association studies using both parent-proband trios and individual TS cases. These collections served as the basis for the first TS GWAS and parallel CNV analysis.

As it became clear that sample size is the major hindrance to gene discovery for complex neuropsychiatric traits, the TAAICG added additional recruitment sites and novel recruitment and assessment methods, such as web-based assessments of previously diagnosed TS cases and remote DNA collection using commercial laboratories across the US. These online protocols facilitated the collection of 1,600 independent TS cases over the course of 2 years, a sample that served as the basis for the second TS GWAS, and CNV studies whose preliminary results were presented at the 1st World Congress on Tourette Syndrome and Tic Disorders.

Each of these large-scale TS genetic studies has relied heavily on extended collaborations and data sharing, both within the TAAICG as well as across additional US and European research groups. The Gilles de la Tourette Syndrome GWAS Replication Initiative (GGRI) consists of multiple TS research groups across the USA, Canada, France, Germany, Austria, Hungary, Italy, Greece and Poland, and formed out of an NIH TS Genetics Workshop following completion of the first TS GWAS. The GGRI collaborative resulted in both the targeted replication study described above and acted
as another major contributing source for the second international TS GWAS and CNV studies. Similarly, TIC Genetics has contributed data from over 400 TS parent-proband trios to the latest TS GWAS. TAAICG and TIC Genetics also are currently collaborating in a joint analysis of exome sequencing data aimed at identifying recurrent, de novo mutations in TS parent-proband trio families.

Most recently, all of the above collaborative groups also have contributed their GWAS data to the Psychiatric Genomics Consortium (PGC) and formed the TS component of the TS and OCD Working Group of the PGC.

2. TAA Neuroimaging Consortium

The TAA Neuroimaging Consortium (TANIC) was established in 2009 with a TAA grant of $500,000, a gift from the Ahmanson Foundation\textsuperscript{11,49}. The TANIC is a multi-site collaborative project led by Bradley Schlaggar, M.D., Ph.D. and Kevin Black, M.D. at the Washington University School of Medicine (St. Louis, MO). The 4 other participating research sites in the consortium are:

- New York University (New York, NY) under the direction of F. Xavier Castellanos, M.D., Michael Milham, M.D., Ph.D., and Adriana Di Martino, M.D.
- Johns Hopkins University/Kennedy Krieger Institute (Baltimore, MD) under the direction of Harvey Singer M.D. and Stewart Mostofsky, M.D.
- The University of California, Los Angeles (LA) under the direction of John C. Piacentini, Ph.D. and James T. McCracken, M.D.
- Mount Sinai School of Medicine (New York, NY) under the direction of Barbara Coffey, M.D., M.S.

The TANIC aims to use MRI and other imaging techniques to determine the brain changes underlying tics in individuals with TS and other Tic Disorders. Researchers from the aforementioned institutions shared MRI scans from hundreds of children with or without a chronic Tic Disorder and the first report from the TANIC examined brain structure in over 200 children. White matter volume was lower in TS in the orbital and medial prefrontal cortex, while gray matter volume was increased in TS in the hypothalamus and posterior thalamus. These brain regions are involved in various processes, including awareness of internal body sensations, which is important given the occurrence of premonitory sensations that precede tics in many patients. Further research using MRI and other methods will clarify exactly how and when these abnormalities develop in TS.

Research by the neuroimaging consortium has opened new avenues for continued research to understand the causes of tics, and has also revealed new brain targets which will be exploited in the future to develop novel treatments for TS.

3. TAA International DBS International Registry

The TAA International Deep Brain Stimulation (DBS) Registry was established in 2011 with the aim of advancing the development and FDA approval of this promising surgical treatment for severe forms of TS\textsuperscript{32,33,50}. The HIPAA-compliant database project is led by Michael Okun, M.D. at the University of Florida (Gainesville, FL) under a joint agreement with the TAA, and supported by grants from the TAA and Medtronic, Inc. ($375,000). The project has attracted over 100 physicians, neurosurgeons, scientists and other experts from 31 institutions across 9 countries. At present, the database has collected medical, surgical, and adverse event data from 163 TS patients who have undergone DBS treatments around the world.
J: FOSTERING COLLABORATIONS BY BUILDING CONSORTIA

Data from the DBS registry are being utilized to answer a range of questions, including the appropriate age for surgery, the optimal brain target for an individual patient, and the best practices for programming, medication management and the best approach to limit adverse events. Thus far, analyses of collected data have led to the publication of improved guidelines for the use of DBS, and a pending publication will report on significant clinical benefits and other outcome data of this treatment approach.

4. TAA Behavior Sciences Consortium

In 2001, the TAA formed a Behavioral Sciences Consortium comprising several clinicians and scientists. The group was asked to develop and test a nonpharmacological treatment for TS. The TAA invested approximately $300,000 to support several planning meetings and small pilot studies, which resulted in the conceptualization of Comprehensive Behavioral Intervention for Tics (CBIT).

The TAA BSC subsequently obtained over $8 million from NIMH to support further research and development of CBIT. The group has since published several research papers on CBIT, including 2 clinical trials demonstrating the ability of this treatment approach to reduce tics in children and adults with TS.

The TAA BSC is continuing its work to further develop CBIT, including efforts to improve patient compliance as well as to modify CBIT so that it can be adopted by diverse professionals (e.g., occupational therapists). Novel methods of delivery also are being explored, notably telemedicine and self-help/home-based approaches, to increase patient access to CBIT, particularly in underserved regions of the US.

5. TAA International Consortium for Medical Cannabis and Related Disorders in Tic Disorders

There is increasing interest in medical cannabis (marijuana) as a potential treatment for tics and other symptoms in TS. This is based on reports by both TS patients and care providers following self-administration by individuals with the disorder. In addition, research has shown that various formulations of medical cannabis or chemical agents acting on the endogenous brain cannabinoid systems can alter TS-related motor activity and behaviors in experimental animals. Thus, the TAA is continuing to fund and otherwise support research in this area in the US and overseas (see grants database). Further, the TAA and others are participating in advocacy efforts in the US and abroad to ease restrictions and regulations to facilitate research into and the use of medical cannabis as a treatment for TS.

Given the diverse interests in exploring and developing medical cannabis as a treatment for TS, the TAA is now seeking to coordinate and lead these efforts through the establishment of an “International Consortium for Medical Cannabis and Related Drugs in Tic Disorders” (TAA ICMCT). This consortium will be comprised of researchers, clinicians, advocates, an others from the US, Canada, Europe and other countries working collaboratively to advance research and policy in this area. Indeed, such international partnership is necessary to drive this field considering the wide variability across countries in the ease or permissibility of research studies.

The TAA ICMCT is being modeled from other successful TAA consortia, i.e. the International DBS Registry, International Consortium on Genomics, Behavioral Sciences Consortium and Neuroimaging Consortium, and is expected to drive research in this potential treatment for TS in the years ahead.
K: CREATING PARTNERSHIPS

From its inception, the TAA has recognized the importance of collaboration with other entities to drive its mission of making life better for all people affected by Tourette and Tic Disorders. Thus, the organization has developed many partnerships with federal and non-federal entities, pharmaceutical and medical device companies, academic institutions, medical and healthcare facilities within the US and overseas. These partnerships have led to major funding for TS research, key scientific advances, dissemination of authoritative information, expert education and trainings, and the approval of new treatments for the TS. Some of the TAA’s key partners include:

1. Federal Institutes

National Institutes of Neurological Disorders and Stroke
The TAA and NINDS developed a cooperative funding agreement, resulting in over $10 million in U01 and ARRA research grants from NINDS, to support the work of the TAA International Genomics Consortium.

National Institutes of Mental Health
The TAA Behavioral Sciences Consortium was awarded over $8 million from NIMH to support the development of CBIT, a non-medication treatment for tics.

Centers for Disease Control and Prevention
The TAA and CDC have an ongoing partnership in which the CDC has for the past 13 years funded (up to $900,000 annually, over $10 million total) a TAA-managed educational program. This program develops educational materials and implements training programs for both lay and professionals across the US.

2. Foundations and Institutions

American Brain Foundation/American Academy of Neurology
The TAA and ABF/AAN have developed a co-funding relationship in which both organizations contribute to fund 1 or 2 fellowships annually, each for $150,000, to support the training and work of early stage clinicians who are interested in TS. This partnership has thus far funded the following projects:

Matthew Capriotti, PhD / San Jose State University
Project Title: Incorporating TeleCBIT into a Hospital-based Tic Clinic

Joseph McGuire, PhD / University of California Los Angeles
Project Title: Neurocognitive Predictors and Neural Correlates of Behavior Therapy for Tourette Syndrome

Flint Espil, PhD / Stanford University
Project Title: Cortical Functioning and Correlates of Behavior Therapy for Youth with Persistent Tic Disorders

Harvard Brain Tissue Resource Center
The TAA has a longstanding partnership with the HBTRC at the McLean Hospital (Belmont, MA) which houses and manages our organization’s collection of valuable brain tissues for research. This collection has been used to discover important brain changes in TS.

National Organization for Rare Disorders
The TAA has had a long and collaborative history working with the NORD to advance the causes of disorders that occur relatively infrequently.
K: CREATING PARTNERSHIPS

Lupin Foundation

The Lupin Foundation has provided funding which has been used to support the organization’s research grants program.

Ahmanson Foundation

The TAA is thankful to have received a gift of $500,000 from the Ahmanson Foundation to support the establishment of the TAA Neuroimaging Consortium. The project aims to use MRI and other imaging techniques to determine the brain changes underlying tics in individuals with TS and other Tic Disorders. The TANIC has already made significant discoveries of brain abnormalities in TS and point to novel targets that might be explored to develop new treatments for the disorder.

3. Pharmaceutical and Medical Devices Industry

Medtronic, Inc

Medtronic has provided a $375,000, 5-year grant to support the development of the TAA International DBS Registry which seeks to advance the development and FDA-approval of this promising surgical treatment for severe forms of TS.

Otsuka Pharmaceutical, Inc.

The TAA worked extensively with Otsuka Pharmaceutical to drive recruitment of participants for its studies of Abilify as a treatment for Tourette. These clinical trials were highly successful and led the FDA to approve Abilify as a treatment for Tic Disorders.

Psyadon Pharmaceuticals, Inc

In 2011, the TAA established a partnership with Psyadon Pharmaceuticals, Inc. to advance the development of ecopipam, a novel D1 antagonist, as a treatment for TS. The TAA provided a grant of $225,000 to Psyadon to commence an open-label trial of the ecopipam in a small group of patients with moderate-severe tics. The trial, which might not have started without TAA-support, was successful and the drug demonstrated significant benefits with few mild adverse effects. Based on these initial positive results, Psyadon initiated a 2nd, randomized, placebo-controlled, clinical trial of ecopipam in a larger population of individuals with the disorder. The drug once again demonstrated significant clinical benefits and relatively mild side effects. Psyadon is now seeking to conduct further clinical trials of ecopipiam which hopefully will lead to the FDA-approval of the drug as a treatment for TS.

Teva

Teva has provided the TAA over $25,000 to support the organization’s research grants program.

Abide Therapeutics

The TAA supports Abide in their efforts to develop effective drugs as potential treatments for TS. Abide generously provided the TAA with a $25,000 sponsorship.

Neurocrine Bioscience and others

The TAA is currently working with other pharmaceutical companies to assist with the recruitment of subjects for clinical trials of various drugs which have the potential to be effective treatments for TS. The TAA is also thankful to have received various levels of sponsorships from these companies which has been used to support the organization’s research programs.
The TAA has established an international network of experts and thought leaders who advise the organization on all research related matters. Indeed, the TAA’s research and medical programs have been developed, implemented and assessed under the guidance of hundreds of experts drawn from Tourette and other fields. These individuals have voluntarily provided expertise, resources and time to the organization over its 45 year history to drive research and discovery in TS and related conditions.

The programs, advances and impact outlined in this document are attributed to the selfless contributions of the TAA’s advisors in the US and abroad. Thus the TAA, BOD and the broader community of people served, are thankful to the following and hundreds of unlisted advisors for their selfless and countless contributions to the mission of making life better for all people impacted by TS and Tic Disorders.

Scientific Advisory Board

The SAB comprises experts from all areas of biomedical and clinical research, and has guided the TAA in reviewing and recommending research grants and other projects for funding by our organization. The SAB also works with the TAA to set funding priorities and advises the TAA on the interpretation of scientific discoveries. The SAB has been led by the following individuals:

1986 – 1987: Thomas N. Chase, M.D.
1992 – 1996: Anne B. Young, M.D., Ph.D.
1997 – 2005: Neal R. Swerdlow, M.D., Ph.D.
2006 – 2010: Peter Hollenbeck, Ph.D. and Jonathan Mink, M.D., Ph.D.
2011 – 2016: Tamara Hershey, Ph.D. and Jonathan Mink, M.D., Ph.D.
2016 – Present: Carol Mathews, M.D. and Peggy Nopoulos, Ph.D.

Medical Advisory Board

The MAB guides the development and management of the TAA’s policies and programs aimed at improving diagnosis, care and treatment of people with TS. The MAB also assists the TAA with providing authoritative answers to our membership, media, public, etc., on a wide range of medical and other issues relating to TS. The MAB has been led by the following individuals:

2007 – 2012: John T. Walkup, M.D.
2012 – 2013: Michael S. Okun, M.D. and John T. Walkup, M.D.
2017 – Present: Barbara Coffey, M.D. and Keith Coffman, M.D.
L: GLOBAL NETWORK OF ADVISORS AND THOUGHT LEADERS

Centers Of Excellence Advisory and Review Committee

The CofE ARC plays a central role in advising the TAA on the development, implementation and oversight of the CofE program. This board is diverse, comprising scientists, clinicians, TAA chapter/support group leaders and members of the TAA Board of Directors.

Carol A. Mathews, M.D. - University of Florida, Gainesville, FL
Douglas Woods, Ph.D. - Marquette University, Milwaukee, WI
Peter Hollenbeck, Ph.D. - Purdue University, West Lafayette, IN
Eric B Nestler, M.D., Ph.D. - Mount Sinai School of Medicine, New York, NY

Kevin Black, M.D. - Washington University in St. Louis, St. Louis, MO
Ruth Bruun, M.D. - Private Practice Psychiatrist, NY
Andrea Cavanna, M.D., Ph.D. - University of Birmingham, Birmingham, United Kingdom
Gerald Erenberg, M.D. - Cleveland Clinic, Cleveland, OH
Bradley Schlaggar, M.D., Ph.D. - Washington University in St. Louis, St. Louis, MO
Reid Ashinoff - TAA Board of Directors
Paul Devore - TAA Board of Directors
Monte Redman - TAA Board of Directors
Randi Zemsky - TAA Board of Directors
Chuck Brackett - TAA Northern California Chapter
Ellie Jarvie, LCSW, CSAC - TAA Wisconsin Chapter

Epidemiology and Prevalence

The TAA is expertly guided on matters relating to the occurrence of TS by Lawrence Scahill, MSN, Ph.D. (Emory University, Atlanta, GA)

Other Contributors

The TAA benefits from the advice of many other advisors, thought leaders and researchers who work with the organization on an as needed basis.
TAA support for research has led to key advances in many areas of interest over the past 45 years. These include a better scientific understanding of the causes, brain changes and occurrences of Tic Disorders; increased education and training of care providers to improve diagnoses and management of the conditions; and the development of effective treatments for patients. However, many unmet needs remain. For example:

- We need to identify other genes and environmental/lifestyle factors that cause or increase the risk of developing Tic Disorders.
- It is important to garner better estimates of the prevalence and regional distribution of Tic Disorders among children and adults. This will help to identify potential risk factors, economic impact, and to attract support to develop programs to meet the needs of all people living with TS and related disorders.
- We must accelerate the education and training program of professions on TS, especially in underserved areas, to further reduce the difficulties people experience in trying to find skilled care providers.
- There continues to be a need for more effective and accessible treatment choices with fewer side effects, including medical, behavioral, surgical and novel treatment approaches.

In the years ahead, the TAA will further develop its successes, address unmet needs, explore emerging opportunities and open new avenues of research and development. These efforts will drive and fulfill the organization’s mission to make life better for all people affected by TS and Tic Disorders.
The following key publications and other references represent vital developments and milestones in the 45-year history of the TAA’s research and medical programs.

Section C: Scientific Discoveries


Section D: Treatment Advances


34. TAA Grants Database https://www.tourette.org/grant-database/

35. ClinicalTrials.gov identifier: NCT02067819
   https://clinicaltrials.gov/ct2/show/record/NCT02067819?term=tourette+orthotic&rank=1

36. TAA Centers of Excellence Program https://www.tourette.org/about-tourette/overview/centers-of-excellence/
Section F: Advances and Consensus In Understanding Of The Nature And Occurrence Of Tic Disorders


Section G: Education And Training

42. TAA Medical and Allied Professional Listing https://www.tourette.org/find-a-doctor/

43. 1ST World Congress on Tourette and Tic Disorders http://touretteworldcongress.org/

Section I: Development of Research Resources and Infrastructures


45. Patient Recruitment Program https://www.tourette.org/research-medical/current-research-programs/

46. TAA Gene Sample Collection https://www.findtsgene.org

Section J: Fostering Collaborations By Building Consortia

47. TAA International Consortium For Genetics https://www.findtsgene.org


49. Neuroimaging Consortium (www.tourette.org/NIC)

50. TAA International DBS Registry https://www.tourette.org/research-medical/deep-brain-stimulation-overview/

O: ACKNOWLEDGEMENTS

The research projects, advances and accomplishments described in this document were and are attributed to the thousands of individuals, families, volunteers, members, companies, organizations, federal institutes, researchers, scientists, physicians and others who have donated monies, time, expertise and other resources to facilitate the various research programs. These achievements were driven and supported by the TAA Board of Directors, Chapters, Support Groups, Staff and Advisory Boards. The TAA is thankful to all those who have and continue to contribute to the mission of making life better for all people impacted by Tourette, Tic and related disorders.
There are many ways to support the Tourette community. Your involvement in our events, contributions, and volunteerism helps ensure that the Tourette Association of American can continue its work in making life better for all people affected by Tourette and Tic Disorders. Visit Tourette.org to learn more today.
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