2014

Progress in research on Tourette syndrome

Kevin J. Black
Washington University School of Medicine in St. Louis

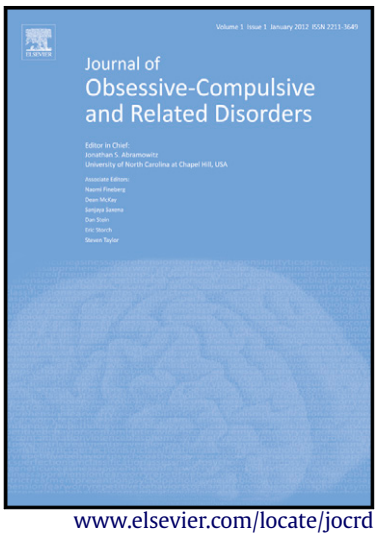
Joseph Jankovic
Baylor College of Medicine

Tamara Hershey
Washington University School of Medicine in St. Louis

Kevin St. P McNaught
Tourrette Syndrome Association

Jonathan W. Mink
University of Rochester

See next page for additional authors



www.elsevier.com/locate/jocrd

Progress in research on Tourette syndrome

Kevin J. Black, Joseph Jankovic, Tamara Hershey, Kevin St. P. McNaught, Jonathan W. Mink, John Walkup

PII: S2211-3649(14)00022-0
DOI: http://dx.doi.org/10.1016/j.jocrd.2014.03.005
Reference: JOCRD146

To appear in: *Journal of Obsessive-Compulsive and Related Disorders*

Received date: 28 February 2014
Accepted date: 12 March 2014

Cite this article as: Kevin J. Black, Joseph Jankovic, Tamara Hershey, Kevin St. P. McNaught, Jonathan W. Mink, John Walkup, Progress in research on Tourette syndrome, *Journal of Obsessive-Compulsive and Related Disorders,* http://dx.doi.org/10.1016/j.jocrd.2014.03.005

Progress in research on Tourette syndrome

Kevin J. Black, M.D. (1) *

Joseph Jankovic, M.D. (2)

Tamara Hershey, Ph.D. (3)

Kevin St. P. McNaught, Ph.D. (4)

Jonathan W. Mink, M.D., Ph.D. (5)

John Walkup, M.D. (6)

(1) Departments of Psychiatry, Neurology, Radiology, and Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO

(2) Department of Neurology, Baylor College of Medicine, Houston, Texas

(3) Departments of Psychiatry, Neurology, and Radiology, Washington University School of Medicine, and Department of Psychology, Washington University, St. Louis, MO

(4) Tourette Syndrome Association, Bayside, NY

(5) Departments of Neurology, Neurobiology and Anatomy, Brain and Cognitive Sciences, and Pediatrics, University of Rochester, Rochester, NY

(6) Division of Child and Adolescent Psychiatry, Department of Psychiatry, Weill Cornell Medical College and New York-Presbyterian Hospital, New York, NY

*Direct questions to this author, at kevin@WUSTL.edu

Progress in research on Tourette syndrome

ABSTRACT

Tourette syndrome (TS) is a heritable neuropsychiatric disorder commonly complicated by obsessions and compulsions, but defined by frequent unwanted movements (motor tics) and vocalizations (phonic tics) that develop in childhood or adolescence. In recent years, research on TS has progressed rapidly on several fronts. Inspired by the Fifth International Scientific Symposium on Tourette Syndrome, the articles in this special issue review advances in the phenomenology, epidemiology, genetics, pathophysiology, and treatment of TS.

INTRODUCTION

Tourette syndrome (TS) is defined by chronic, but variable, unwanted movements (motor tics) and sounds (phonic tics) that develop spontaneously in childhood or adolescence. However, this relatively simple definition neither conveys the breadth of clinical symptoms and disability that TS can produce in patients nor explains the fascination TS has evoked in physicians, scientists, and the general public.

Research on TS has grown increasingly rapidly over the past several decades (see Figure 1). The Tourette Syndrome Association, which provided much of the preliminary funding for these initiatives, has helped disseminate research advances by hosting five International Scientific Symposia on Tourette Syndrome. The most recent such symposium took place on June 12-13, 2009, in New York City. Over 250 experts and delegates from 17 countries attended the meeting, which included 24 plenary lectures, 7 round table discussions and 57 poster presentations.

Several notable studies were presented for the first time at the Fifth Symposium. To give only two examples, Dr. Larry Scahill discussed results of a very large study of the prevalence of medically diagnosed Tourette syndrome in the United States, published only a few days earlier by the U.S. Centers for Disease Control and Prevention (CDC).[1] Dr. Doug Woods reported for the first time the results of one of the largest randomized controlled trials of *any* treatment for tics, which tested the efficacy of a behavioral treatment for tics called CBIT (Comprehensive Behavioral Intervention for Tics); the results generated substantial enthusiasm and discussion and were subsequently published in JAMA.[2] Abstracts and video clips from plenary lectures are available online (http://www.tsa-usa.org/Z_IntSciSymp5/IntlSciSymposTS5_contents.html), as are poster abstracts (http://www.tsa-usa.org/aResearch/images/5thIntlSciSympPosterAbstracts.pdf).

This introductory article will point out highlights of the work presented at the Symposium and introduce the remaining articles, in which speakers from the Symposium provide updated summaries of research in their respective areas of TS expertise. Together, the articles in this special issue comprise a solid introduction to the current state of research on TS. Dr. Andrea Cavanna first discusses the phenomenological, genetic and other features that link TS and obsessive-compulsive disorder,[3] followed by a review of the phenomenology of tic disorders by Dr. James Leckman and colleagues.[4]

TS RESEARCH HIGHLIGHTS

The known heritability of TS provides tantalizing potential for progress in understanding its causes and pathophysiology. At the Symposium, Dr. Nelson Freimer reviewed the current state of genetics research in TS, including results from multisite collaborative studies of sib pairs and large multigenerational families, which together involved DNA from over 2,000 individuals.[5] A locus on the short arm of

chromosome 2 was most robustly linked to susceptibility to TS. Genome-wide association studies were being analyzed, with preliminary evidence for several strong signals that were being followed up for specificity. Combined studies with OCD symptoms in TS probands and vice versa were promising leads. Some of the studies discussed have published results since the meeting.[6-8] Dr. Jim Hudziak reported on a genetic study of a large sample of children (30,000+). This study showed strong evidence for high heritability of tics (explaining 69-78% of the variance), with environmental effects limited to those unique to each individual rather than those environmental effects shared by family members. In this issue, Dr. David Pauls and colleagues update the status of the search for the genes responsible for the high heritability of TS.[9, 10]

Other presentations focused on the physiology of tic disorders, a topic reviewed comprehensively elesewhere.[11-16] Dr. Suzanne Haber discussed research on the anatomy of the basal ganglia, focusing on how the organization of its connections with the cortex of the brain may underlie the development of both normal and abnormal movements. Dr. Flora Vaccarino discussed her exciting research findings on the substantial (~50%) loss of certain interneurons in the striatum in postmortem brain samples from people who had TS during life. Dr. Joshua Berke discussed his research into the function of these interneurons and their response to behavioral tasks and drugs that affect dopaminergic neurotransmission. Dr. Bradley Schlaggar discussed important results from his laboratory's brain imaging studies in TS, which show a difference in TS in the patterns of simultaneous, spontaneous fluctuations in the activity of different regions of the brain (functional connectivity). Drs. Jessica Church and Schlaggar place that work in context of other neuroimaging findings in a report in this issue[17, see also 18] Presentations by Drs. Barak Caine and Joseph Garner discussed potential translational science approaches using animal models to understand the cause and physiology of tics or to rapidly screen potential new treatments.

Another Symposium session focused on public health and the connections between science, patients and the public. Dr. Larry Scahill presented data from the CDC epidemiological study mentioned above;[1] for this issue, he and his colleagues summarize recent studies on the prevalence of TS.[19] Dr. John Walkup reported on information on "real-life" TS treatment from two large samples, one from Medicaid and one from private insurers.[8] The results suggest that many children with tics do not get medical attention, and that those who do present to clinicians have substantial comorbidity. Dr. Anne-Liis von Knorring reported on comorbid symptoms in tic patients from community samples. In clinical samples, biases were suspected to have inflated the rate of comorbid psychological symptoms. However, even in her community samples of TS or chronic motor/vocal tic disorder, almost all children (92%) had at least one psychiatric diagnosis in addition to the chronic tic disorder. Dr. Doug Woods presented results of a survey of 741 adults with tics or parents of children with tic disorders. The survey revealed that treatment actually being received does not reflect current standards of care. For instance, haloperidol was the most common treatment for adults, and although habit reversal (HRT) or CBIT is well proven to be effective, almost no patients had been treated with it; in fact, in terms of number of patients treated, HRT/CBIT came in 6th place, after 5 unproven psychotherapies including relaxation. This finding probably reflects in part a need to better inform physicians of the treatment's efficacy, but other possible explanations include a shortage of trained HRT/CBIT therapists and the fact that clinical trials participants do not represent the full range of patients seen in clinical settings (e.g. research studies require a patient and parent who can comply with the treatment protocol).

A session on neuroimmunology provoked vigorous debate. Speakers included Drs. Tanya Murphy, Michael Schwartz, Gavin Giovannoni, Roger Kurlan, and James Leckman. Although new data continue to raise interesting questions about the association of psychological stress, infections with Group A streptococci or other pathogens, immune markers, and current symptom status, substantial disagreement remained after the session on several key issues. Chief among these were questions about

the direction of causality of these associations, their specificity, and whether any direct causative relationship between infectious response and symptoms pertained to few or many patients with TS.

One attempt to address the controversy surrounding pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) has been the proposal of a new entity, termed Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).[20] In contrast to PANDAS, the diagnostic criteria for PANS reduce the focus on tics by requiring "abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake" rather than "presence of [OCD] or a tic disorder," and by excluding patients whose symptoms are "better explained by … Tourette disorder." However, tics are retained in the PANS criteria as one of several "additional neuropsychiatric symptoms, with similarly severe and acute onset,"[20] and the validity and utility of this new proposed diagnosis will continue to be studied.

The first step in the management of patients with TS is proper education of the patient, family members, teachers, and other individuals who frequently interact with the patient about TS. They should be encouraged to work together to provide the best therapeutic approach and implement behavioral, pharmacological, and, if necessary, surgical therapy to target the most troublesome symptoms. While the selection of the treatment option should be evidence-based, each individual is different and, therefore, the treatment must be tailored specifically to the needs of the individual patient and may also be influenced by the personal preference and experience of the treating physician.[16] At the Symposium, Dr. Veerle Visser-Vanderwalle reviewed deep brain stimulation (DBS) for tics, a treatment that may be appropriate for certain very carefully selected patients.[21] The Tourette Syndrome Association has sponsored the creation of an international database for DBS in TS (http://dbs.tsa-usa.org/). DBS also may provide insights into brain regions that may affect tic severity.[14,

[22] Similar insights were offered in a review of pharmacological treatments for TS by Drs. Donald Gilbert and Joseph Jankovic. Articles in this issue update both presentations.[23, 24]

Finally, the Fifth Symposium for the first time devoted a session to behavior therapy of tics. Dr. Adam Aron discussed research into how the brain manages the volitional control of movement. Dr. Alan Peterson discussed misunderstandings of behavior therapy as applied to TS. Specifically, he clarified that modern behavior therapists understand that TS is caused largely by one's genes, but that manipulations of the environment affect momentary and situational tic severity. "Behavior therapy for tics is *not* a cure, but a management strategy that can help people live a better life." He also summarized research debunking myths that HRT/CBIT would lead to rebound worsening of tics or to substitution of new tics for those targeted in treatment. Dr. Cara Verdellen described her research and clinical experience with exposure and response prevention (E/RP) as an alternative behavioral therapy for tics, inspired by its success in OCD. Finally, Drs. Doug Woods and John Piacentini reported and discussed the results of the multi-site randomized controlled trial (RCT) of CBIT versus a nonspecific psychological therapy in 126 children with TS.[2] An RCT of CBIT in adults with TS, using the same study design and a similar sample size, has since been completed.[25] Each of these CBIT studies is among the largest RCTs ever conducted for TS.[26]

A LOOK FORWARD

In the Fifth Symposium's opening session, Dr. John Walkup provided a provocative discussion of the novel implications of the results of the CBIT trial. He pointed out that these results might lead to several paradigm changes in how patients, family members, and treating clinicians think about TS and its treatment (see http://www.tsa-usa.org/Z_IntSciSymp5/Session1/VideoPlayer.html; compare Figure 2).

Dr. Walkup acknowledged that recognizing the efficacy of behavioral strategies for tics can cause uncomfortable paradigm shifts for some, or misunderstandings by others, but he highlighted how this recognition can also empower patients and families.

Time will tell how prescient or premature these predictions prove to be, but one hopes that they point in the general direction of an appropriate correction to how TS is viewed by patients, physicians and the general public. In the 1970s and 1980s, the discovery that medications could substantially improve TS symptoms led to one of the defining missions of the nascent Tourette Syndrome Association: a vigorous defense against the then-prevalent (but empirically unsupported) view that tics resulted from psychologically immature responses to sexual drives or noxious early-life experiences, and should be treated by insight-oriented psychotherapy. The TSA's focus on biological therapy was widely adopted by physicians into the first decade of the new millennium; it helped many patients find appropriate treatment, reduced societal stigma, and helped drive important research. However, this focus also fostered over-corrections at times, such as assertions by some writers that "[all] psychotherapy is useless" for tics, or implications that only neurologists should manage TS. With these writers, the pendulum had swung a little too far. After all, tics are influenced by social context, they differ from other abnormal movements in part by suppressibility and a perception of volitional control,[16, 27] and for many TS patients tics are not the most troubling symptom.[28]

Fortunately this tunnel vision was not universal; for instance, the TSA funded some of the earliest rigorous research on behavior therapy for tic treatment, encouraged continued research on non-tic manifestations of TS, and provided crucial support for the Behavioral Science Consortium's creation and the recent CBIT efficacy trials. The TSA has also recognized that expertise in TS extends beyond guild boundaries: the organization's Medical Advisory Board has predominantly been staffed by neurologists and psychiatrists, but psychology, nursing, and other fields have also contributed. The editors of the

Fourth Symposium's report rejected a suggestion that TS should be reclassified as a purely neurological disorder, in favor of a more balanced view: "At the moment, the placement of TS in the psychiatric sphere of nosology seems stable, although debatable; in the future, we hope there will be a new perspective that will eliminate the need for such an either-or designation."[29]

The developments in TS research reviewed in the following articles only strengthen this view. Hopefully the upcoming Sixth International Symposium on Tourette Syndrome will report not only breakthroughs in research but also wider acceptance of a balanced, empirically based view of TS. Such acceptance would include openness to evidence-based treatments whether psychological, pharmacological or surgical, an approach that will continue to invite collaboration of clinicians and researchers from diverse fields of expertise.

REFERENCES

1. Scahill L, Bitsko RH, Visser SN. Prevalence of diagnosed Tourette Syndrome in persons aged 6-17 Years - United States, 2007. Morbidity and Mortality Weekly Report 2009;58:581-585.

2. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010;303(19):1929-1937.

3. Cavanna A. Tourette syndrome and obsessive-compulsive disorder. J Obsessive Compuls Relat Disord 2014;this issue.

4. Leckman JF, King RA, Bloch MH. Clinical features of Tourette syndrome and tic disorders. J Obsessive Compuls Relat Disord 2014;this issue.

5. Tourette Syndrome Association International Consortium for Genetics. Genome scan for Tourette disorder in affected-sibling-pair and multigenerational families. American Journal of Human Genetics 2007;80(2):265-272.

6. Crane J, Fagerness J, Osiecki L, et al. Family-based genetic association study of DLGAP3 in Tourette Syndrome. Am J Med Genet B Neuropsychiatr Genet 2011;156B(1):108-114.

7. Knight S, Coon H, Johnson M, Leppert MF, Camp NJ, McMahon WM. Linkage analysis of Tourette syndrome in a large Utah pedigree. Am J Med Genet B Neuropsychiatr Genet 2010;153B(2):656-662.

8. Olfson M, Crystal S, Gerhard T, Huang C, Walkup JT, Scahill L. Patterns and correlates of tic disorder diagnoses in privately and publicly insured youth. Journal of the American Academy of Child and Adolescent Psychiatry 2011;50(2):119-131.

9. Pauls DL, Fernandez TV, Scharf JM, State MW. The inheritance of Tourette's disorder: A review. Movement Disorders 2012;(this issue).

10. Deng H, Gao K, Jankovic J. The genetics of Tourette syndrome. Nat Rev Neurol 2012;8(4):203-213.

11. Leckman JF, Vaccarino FM, Kalanithi PS, Rothenberger A. Annotation: Tourette syndrome: a relentless drumbeat--driven by misguided brain oscillations. JChild PsycholPsychiatry 2006;47(6):537-550.

12. Albin RL. Neurobiology of basal ganglia and Tourette syndrome: striatal and dopamine function. Adv Neurol 2006;99:99-106.

13. Plessen KJ, Bansal R, Peterson BS. Imaging evidence for anatomical disturbances and neuroplastic compensation in persons with Tourette syndrome. J Psychosom Res 2009;67(6):559-573.

14. Leckman JF, Bloch MH, Smith ME, Larabi D, Hampson M. Neurobiological substrates of Tourette's disorder. J Child Adolesc Psychopharmacol 2010;20(4):237-247.

15. Basal ganglia anatomy, biochemistry, and physiology. In: Singer HS, Jankovic J, Mink JW, Gilbert DL, eds. Movement Disorders in Childhood. Philadelphia, PA: Saunders Elsevier, 2010:2-8.

16. Jankovic J, Kurlan R. Tourette syndrome: evolving concepts. Mov Disord 2011;26(6):1149-1156.

17. Church JA, Schlaggar BL. Pediatric Tourette syndrome: Insights from recent neuroimaging studies. Movement Disorders 2012;(this issue).

18. Greene DJ, Black KJ, Schlaggar BL. Neurobiology and functional anatomy of tic disorders. In: Martino D, Leckman JF, eds. Tourette Syndrome. Oxford: Oxford University Press, 2013.

19. Scahill L, Specht M, Bradbury K. The prevalence of TS and clinical characteristics in children. Movement Disorders 2012;(this issue).

20. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatrics & Therapeutics 2012;3:113.

21. Mink JW, Walkup J, Frey KA, et al. Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. Movement Disorders 2006;21(11):1831-1838.

22. Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, Jankovic J. Deep brain stimulation for Tourette syndrome: target selection. Stereotact Funct Neurosurg 2012;90(4):213-224.

23. Visser-Vandewalle V, Neuner I, Zrinzo L, Kuhn J, Okun MS. Deep brain stimulation for Tourette syndrome: The current state of the field. Movement Disorders 2012;(this issue).

24. Gilbert DL, Jankovic J. Pharmacological treatment of Tourette syndrome. Movement Disorders 2012;(this issue).

25. Wilhelm S, Peterson AL, Piacentini J, et al. Randomized trial of behavior therapy for adults with Tourette syndrome. Arch Gen Psychiatry 2012;69(8):795-803.

26. Black KJ. Behavior therapy for Tourette syndrome. 2012. http://tourette.wikispaces.com/CBIT_for_tics

27. Black KJ. Tics. In: Kompoliti K, Verhagen Metman L, Comella C, et al., eds. **Encyclopedia of Movement Disorders**. Oxford: Elsevier (Academic Press), 2010:231-236.

28. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol 2000;42(7):436-447.

29. Cohen DJ, Jankovic J, Goetz CG. Preface. Advances in Neurology 2001;85:xxi-xxiv.

FIGURE 1. Cumulative number of published articles on Tourette syndrome and other tic disorders as of the dates of each of the five International Scientific Symposia on Tourette Syndrome (circles) and 28 Feb 2014. The dashed line is the best-fit quadratic curve to these 6 data points ($r > 0.999$). PubMed was searched for ("Tic Disorders"[MeSH] OR Tourette), limited to the relevant publication date ranges.

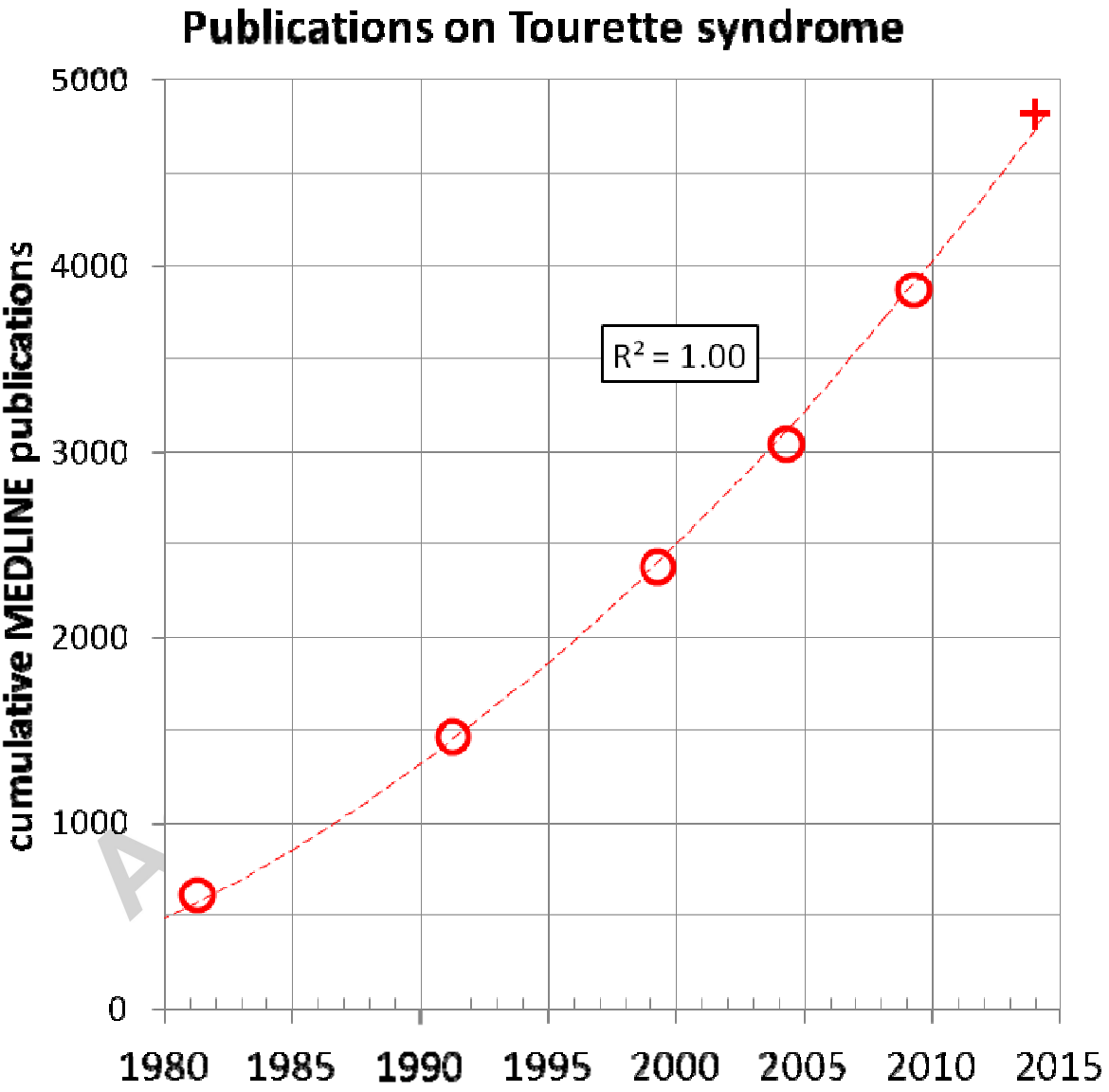


TABLE 1. Paradigm shift in TS treatment suggested by the success of CBIT (table from John C. Piacentini, Ph.D.)

Old paradigm	New paradigm
Ignore your tics	Become more aware of your tics
Tics can't be controlled	Learn to manage tics
Don't punish	Reward efforts to manage tics
Don't try to suppress tics	Use behavioral strategies
Tics and urges to tic get worse when you suppress	Tics and urges improve with behavioral treatment
Suppressing one tic makes new tics develop	New tics don't develop from behavioral treatment

PROGRESS IN RESEARCH ON TOURETTE SYNDROME

Research Highlights

- Tourette syndrome and OCD overlap partially in terms of genetics and phenomenology
- Articles in this special issue review recent advances in Tourette syndrome research
- This article summarizes presentations at the Fifth International Symposium on TS
- Advances have occurred in epidemiology, genetics, physiology and treatment of TS
- Behavior therapy for tics is effective, but not yet widely adopted in patient care