Title

Childhood Predictors of Long-Term Tic Severity and Tic Impairment in Tourettes Disorder.

Journal

Behavior Therapy, 53(6)

Authors

Woods, Douglas
Espil, Flint
McGuire, Joseph
et al.

Publication Date

2022-11-01

DOI

10.1016/j.beth.2022.07.002

Peer reviewed

HHS Public Access

Author manuscript

Behav Ther. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Behav Ther. 2022 November ; 53(6): 1250–1264. doi:10.1016/j.beth.2022.07.002.

Childhood Predictors of Long-term Tic Severity and Tic Impairment in Tourette's Disorder

Emily J. Ricketts, Ph.D.[a], **Douglas W. Woods, Ph.D.**[b], **Flint M. Espil, Ph.D.**[c], **Joseph F. McGuire, Ph.D.**[d], **Jordan T. Stiede, M.S.**[b], **Jennifer Schild, M.S.**[e,f], **Mina Yadegar, Psy.D.**[g], **Shannon M. Bennett, Ph.D.**[e], **Matthew W. Specht, Ph.D.**[e], **Susanna Chang, Ph.D.**[a], **Lawrence Scahill, M.S.N., Ph.D.**[h], **Sabine Wilhelm, Ph.D.**[i], **Alan L. Peterson, Ph.D.**[j], **John T. Walkup, M.D.**[k,l], **John Piacentini, Ph.D.**[a]

[a]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA 90024

[b]Department of Psychology, Marquette University, Milwaukee, WI 53233

[c]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305

[d]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205

[e]Department of Psychiatry, Weill Cornell Medicine, New York, NY 10065

[f]Department of Psychology, Suffolk University, Boston, MA 02108

[g]Rogers Behavioral Health, Los Angeles, CA 90056

[h]Marcus Autism Center, Emory University School of Medicine, Atlanta, GA 30322

[i]Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA 02114

[j]Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229

[k]Ann and Robert H. Lurie Children's Hospital of Chicago, IL 60611

[l]Pritzker Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL 60611

Abstract

Tics peak in late childhood and decline during adolescence. Yet, for some with Tourette's disorder, tics persist into adulthood. We evaluated childhood predictors of adult tic severity and tic impairment, and change over time. Eighty adolescents/adults were evaluated 11 years

Direct correspondence concerning this article should be addressed to Emily J. Ricketts, Ph.D., University of California, Los Angeles, Department of Psychiatry and Biobehavioral Sciences, 760 Westwood Blvd., Los Angeles, CA; phone: (310) 825-2701; fax: (310) 267-4925; ericketts@mednet.ucla.edu.

following a randomized-controlled trial of behavior therapy. An independent evaluator rated tic severity and tic impairment at baseline, post-treatment, and long-term follow-up. At baseline, parents completed demographics/medical history, and youth tic, internalizing, and externalizing symptom ratings. Youth rated premonitory urge severity and family functioning. After controlling for prior tic treatment effects, female sex and higher tic severity predicted higher tic severity in adulthood; and female sex, no stimulant medication use, higher tic severity, and poorer family functioning predicted higher tic impairment. Higher tic severity and premonitory urge severity predicted smaller reductions in tic severity, whereas higher externalizing symptoms predicted greater reduction in tic severity. Female sex predicted smaller reduction in tic impairment, and externalizing symptoms predicted greater reduction in tic impairment. Female sex and childhood tic severity are important predictors of tic severity and tic impairment in adulthood. Family functioning, premonitory urge severity, and tic severity are important modifiable targets for early or targeted intervention to improve long-term outcomes.

Keywords

tics; course; longitudinal; gender; externalizing

Introduction

Tourette's Disorder (TD) is characterized by abrupt, repetitive movements and/or vocalizations lasting longer than one year (American Psychiatric Association, 2013), and displays male predominance (Hirschtritt et al., 2015). On average, tics emerge between 4 and 8 years and develop rostrocaudally, with initial tics centered around the face and later tics extending to the limbs (Leckman, King, & Bloch, 2014). Following onset, tics steadily rise in severity, peaking at age 10 to 12 years, and decrease during adolescence for many individuals (Bloch & Leckman, 2009; Hirschtritt et al., 2015). Tics range from simple (e.g., eye blinking, nose scrunching, head jerking) to complex (e.g., kicking, jumping, coprolalia, echolalia) in nature, and are often preceded by a localized physical sensation presenting in the body site associated with the tic, generalized bodily sensation, or not-just-right feeling, termed a premonitory urge (Leckman et al., 2014). TD frequently presents with psychiatric comorbidities - particularly attention-deficit/hyperactivity disorder (ADHD), disruptive behavior problems, obsessive-compulsive disorder (OCD), and anxiety (Hirschtritt et al., 2015). TD may result in impairment across an array of life areas, including work, school, and social and family relationships (Conelea et al., 2011; Edwards et al., 2017). First line treatment for TD is behavior therapy for tics administered alone or in combination with alpha agonists and antipsychotic medications; and stimulants are also often prescribed to manage co-occurring ADHD (Pringsheim et al., 2019).

Although tics emerge in childhood and often improve during adolescence, tics can persist or worsen into adulthood. Findings regarding longitudinal tic outcomes from childhood to adulthood have shown that 69% to 82% of patients with TD report improvement in tic severity during late adolescence/early adulthood, with 47% to 69% reporting significant improvement (Burd et al., 2001; Erenberg, Cruse, & Rothner, 1987; Lowe, Capriotti, & McBurnett, 2019). However, tics persist to some degree in 53% to 100% of late adolescent

or adult follow-up samples (Bloch et al., 2006; Byler et al., 2015; Goetz, Tanner, Stebbins, Leipzig, & Carr, 1992; Groth, Debes, Rask, Lange, & Skov, 2017; Leckman et al., 1998; Lowe et al., 2019; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003; Thériault et al., 2018), and at moderate or severe levels in 12% to 24% (Bloch et al., 2006; Goetz et al., 1992; Groth et al., 2017; Leckman et al., 1998). With respect to impairment, 26% to 88% of tic patients endorse tic impairment at long-term follow-up (Byler et al., 2015; Erenberg et al., 1987; Lowe et al., 2019).

However, research to date offers limited information regarding predictors of long-term tic outcomes and change in tic outcomes over time. Examining predictors of outcomes at a given point in time and predictors of the degree of change in outcomes over time may provide distinct information regarding long-term tic outcomes. In fact, evaluating predictors of rate of change has added value, as it provides information regarding factors which may either bolster or hinder symptom improvement over time. Taken together, such knowledge has implications for the application of early and/or targeted intervention in effort to positively influence long-term tic outcomes and trajectories.

There are a range of predictors of tic severity and tic impairment in adulthood. Childhood tic severity has frequently been found to predict tic severity in late adolescence or adulthood (Bloch et al., 2006; Goetz et al., 1992; Groth, Skov, Lange, & Debes, 2019); and both tic severity and the presence of premonitory urges in childhood have predicted impairment in late adolescence or adulthood (Cavanna, David, Orth, & Robertson, 2012). Sex also influences outcomes, as females have shown higher motor tic severity and tic impairment in adulthood and an increased likelihood of worsening global tic severity and tic impairment over time than males (Lichter & Finnegan, 2015). A separate cross-sectional analysis found higher tic severity with advancing age in females relative to males with TD (Garcia-Delgar et al., in press). Also, psychiatric comorbidity may influence long-term outcomes. Interestingly, the presence of ADHD during childhood predicted improvement in tic severity in adulthood in one study (Lowe et al., 2019), but was not predictive of adult tic severity outcomes in another study (Bloch and colleagues, 2009). Further, childhood functional impairment also appears tied to future tic severity, as higher academic impairment during childhood was found to predict greater improvement in tic severity at long-term follow-up (Lowe et al., 2019).

Although informative, most prior studies are limited by a lack of clinician-rated tic outcome measures, lack of inclusion of tic impairment outcomes, limited clinical characterization, limited tracking of treatment obtained since initial assessment, and reliance on retrospective report. In the first systematic, prospective, long-term follow-up study of youth with TD who had received behavior therapy or psychoeducation and supportive therapy through a randomized clinical trial during childhood (Piacentini et al., 2010), participants showed a 40% remission rate for TD diagnosis and substantial decreases in clinician-rated tic severity and tic impairment at a mean 11-year follow-up (Espil et al., in press). In the current study, we utilized this sample to evaluate the childhood predictors of tic severity and tic impairment in late adolescence and early adulthood at 11-year follow-up. Further, we explored childhood predictors of change in tic severity and impairment over time. Based on prior literature regarding long-term predictors of tic outcomes, it was hypothesized that

sex (i.e., female status), tic severity, and premonitory urge severity would significantly predict higher tic severity and tic impairment in late adolescence and early adulthood, and their diminished reduction over time (Cavanna et al., 2012; Groth et al., 2019; Lichter & Finnegan, 2015). Similarly, based on the natural phenomenology of TD (Leckman et al., 2014), it was hypothesized that the following additional baseline characteristics, including comorbidity (internalizing and externalizing symptoms), family functioning, and medication status (tic medication, stimulant medication), would also significantly predict long-term tic severity and tic impairment outcomes.

Method

Participants

Participants were 80 adolescents and adults aged 16 to 30 years (M = 22.87, SD = 2.70) who participated in a long-term follow-up evaluation of the randomized, controlled comparison of CBIT and Psychoeducation and Supportive Therapy (PST) in childhood (Piacentini et al., 2010). Follow-up occurred 11.17 years on average (SD = 1.25; range = 7.08 to 13.67) after participants completed the post-treatment assessment. The sample was predominantly male (n = 60, 75.0%) and non-Hispanic/Latino (n = 73, 91.2%). Participants were of white (n = 69, 86.3%), Black (n = 1, 1.3%), Asian (n = 4, 5.0%), multi-racial (n = 4, 5.0%), and other (n = 2, 2.5%) racial backgrounds. The majority of the sample were single/never married (n = 66, 82.5%) and had attained partial college education or higher (n = 57, 71.3%). Half of the sample were employed (n = 40, 50.0%). YGTSS total tic severity at follow-up was 16.22 on average (SD = 9.54) and YGTSS tic impairment was 10.00 on average (SD = 10.77). The follow-up and full CBIT samples were comparable with respect to baseline characteristics (see Table 1). Just over one-third of the sample (n = 31, 38.8%) reported having received an evidence-based treatment (EBT) for tics (i.e., tic-influencing medication and/or behavior therapy for tics) since completion of the initial trial. The present sample included 38 participants who had originally been assigned to CBIT and 42 who had been assigned to PST. Among follow-up participants who had been assigned to CBIT, 55.6% (n = 21) were treatment responders and 44.7% (n = 17) were non-responders. Among follow-up participants who had been assigned to PST, 14.3% (n = 6) were treatment responders and 85.7% (n = 36) were non-treatment responders. See Espil et al. (in press) for more details.

Measures

The Yale Global Tic Severity Rating Scale (YGTSS).—The YGTSS (Leckman, Riddle, Hardin, Ort, Swartz, Stevenson, & Cohen, 1989) is a gold-standard, clinician-administered, semi-structured interview evaluating tic severity over the past week. The measure includes a checklist of motor and vocal tics, and items assessing number, frequency, intensity, complexity, and interference for both motor and vocal tics. Items are rated on a scale from 0 to 5, with higher scores indicative of higher tic severity. The scale yields independent motor tic and vocal tic scores, which sum to produce a total tic score; and independent tic impairment score. The YGTSS exhibits fair to excellent test-retest reliability, good to excellent internal consistency, interrater reliability, and convergent validity and moderate to excellent discriminant validity (Leckman et al., 1989; McGuire et al., 2018; Storch et al., 2005).

Anxiety Disorders Interview Schedule-IV-Parent Version (ADIS-IV-P).—The ADIS-IV-P (Silverman & Albano, 1996) is a semi-structured diagnostic interview evaluating anxiety disorders and other DSM-IV psychiatric disorders in children ages 6 to 17 years. Diagnostic severity is rated using a 0 (none)- to- 8 (extremely severe)-point clinical severity rating, with ratings of 4 or higher indicating clinical diagnosis. The interview exhibits good to excellent interrater reliability (Lyneham, Abbott, & Rapee, 2007), excellent test-retest reliability (Silverman, Saavedra, & Pina, 2001), and support for concurrent validity (Wood, Piacentini, Bergman, McCracken, & Barrios, 2002).

Demographics and Medical History.—Participants/parents provided demographics and medical history at baseline. At 11-year follow-up, an evaluator assessed treatment utilization since the CBIT trial ended (i.e., treatment received between post-treatment assessment and long-term follow-up assessment), including evidence-based treatment for tics (i.e., tic-influencing medication and/or behavior therapy for tics).

Parent Tic Questionnaire (PTQ).—The PTQ (Chang, Himle, Tucker, Woods, & Piacentini, 2009) is a parent-reported scale assessing child tic severity over the prior week. The measure includes 14 common motor tics and 14 common vocal tics. Parents rate the frequency and intensity of tics present in the past week. Frequency and intensity ratings are summed to produce independent scores for motor and vocal tics. Motor and vocal tic scores sum to yield an overall total tic severity score. The measure displays good to excellent internal consistency, good to excellent test-retest reliability, and good convergent and discriminant validity (Chang et al., 2009; Ricketts et al., 2018); and high agreement across in-person and internet videoconference-delivered modalities (Ricketts et al., 2016).

The Premonitory Urge for Tics Scale (PUTS).—The PUTS (Woods, Piacentini, Himle, & Chang, 2005) is a 10-item self-report scale assessing presence and frequency of premonitory urges to tic. Items are rated on a scale ranging from 1 (not at all true) to 4 (very much). The total score reflects the sum of the first 9 items. Higher scores indicate more severe premonitory urges. The PUTS has demonstrated good internal consistency, strong test-retest reliability, and good concurrent validity (Openneer et al., 2020; Raines et al., 2018; Woods et al., 2005).

The Achenbach Child Behavior Checklist for Ages 6–18 (CBCL/6–18).—The CBCL/6–18 (Achenbach & Rescorla, 2001) is a 113-item parent-report measure assessing child behavioral and emotional functioning over the past 6 months. The CBCL includes 8 syndrome scales, including aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, somatic complaints, social problems, thought problems, and withdrawn/depressed; and externalizing problems, internalizing problems, and total problems scales. The internalizing domain of the CBCL is comprised of the anxious/depressed, withdrawn/depressed, and somatic complaints scales, and the externalizing domain includes the rule breaking behavior and aggressive behavior scales. Total impairment scores are calculated by summing the syndrome scales and 17 additional uncategorized items. Raw scores are converted to norm-referenced T-scores, with higher T scores indicating high externalizing

problems. The CBCL has demonstrated validity and reliability in several psychometric analyses (Albores-Gallo et al., 2006; Ferdinand, 2008; Leung et al., 2006).

The Brief Family Assessment Measure-III (B-FAM-III).—The B-FAM-III (Skinner et al., 1995) is a 14-item abbreviated version of the Family Assessment Measure (FAM)-III. The B-FAM-III includes items evaluating family values, involvement, affective expression, communication, task accomplishment, and role performance (Gardner, Huber, Steiner, Vazquez, & Savage, 2008). Items are summed to yield a total score. Higher scores are indicative of poorer family functioning. Reliability and validity of the parent measure are supported (Skinner, Steinhauer, & Sitarenios, 2000).

Procedure

Participants completed an initial baseline assessment as part of a 10-week clinical trial comparing CBIT and PST (Piacentini et al., 2010) across three sites (University of California, Los Angeles [n = 45], University of Wisconsin-Milwaukee/Marquette University [n = 40] and Johns Hopkins University [n = 41]). As part of this assessment, a trained independent evaluator (IE) assessed psychiatric diagnosis (ADIS-IV-P), tic severity and tic impairment (YGTSS) at pre-treatment. Parents provided participant and family demographic information and medical history, and rated youth tic severity (PTQ), and internalizing and externalizing symptoms (CBCL). Youth rated premonitory urge severity (PUTS), and family functioning (BFAM-III). At post-treatment (10-week), the IE re-rated the YGTSS and completed a global tic-related illness improvement rating since baseline (i.e., Clinical Global Impression – Improvement scale; Guy, 1976). For the current follow-up study, 80 of the original 126 youth (63.4%) from the treatment study were recruited from three sites: UCLA (n = 32), Marquette University (n = 22), and Weill Cornell University (n = 26). Adults provided institutional review board-approved consent for participation. Youth (ages 17 and below) provided assent, with parents of youth providing parent permission, and parents of all age ranges providing consent for their own participation when available. Interviews were completed in person or via web-based videoconferencing depending on participant geographic proximity to the enrollment site. IEs with a Bachelor's degree or higher, trained to reliability and masked to original treatment assignment, administered the YGTSS to all participants.

Statistical Analysis of Baseline Predictors of Long-term Tic Severity and Impairment—There were no significant differences in clinician-rated tic severity or tic impairment across sites at baseline or 11-year follow-up. Therefore, data were combined across sites for analyses. Multiple linear regression with backward elimination was performed to identify the most important baseline variables predicting clinician-rated tic severity and tic impairment at 11-year follow-up, after controlling for potential prior tic treatment effects. Specifically, to account for potential prior tic treatment effects on long-term tic outcomes, initial treatment assignment (CBIT or PST), post-treatment responder status on the CGI-I (i.e., rating of "much improved" or "very much improved"), and any EBT for tics (i.e., tic-influencing medication and/or behavior therapy for tics) received during the period between post-treatment assessment and long-term follow-up assessment were entered as covariates. Four participants were missing data for EBT for tics and were

subsequently coded as having not received such EBT. We collectively refer to these three covariates as prior tic treatment effects. The following baseline predictors were determined a priori and entered together with prior tic treatment effects variables: demographic (i.e., sex), medication status (tic medication, stimulant medication), tic phenomenology (PTQ total, PUTS total), comorbidity (CBCL internalizing and externalizing totals), and family functioning (B-FAM-III total). Dimensional variables were centered prior to entry into the regression model. YGTSS total tic severity and YGTSS impairment at 11-year follow-up were entered as dependent variables in separate yet parallel analyses. Note, parent-reported tic severity (PTQ total) was selected as a baseline predictor rather than YGTSS total tic severity, as clinician-rated tic severity cannot serve as a baseline predictor in analyses of change in clinician-rated tic severity from baseline to long-term follow-up due to shared variance.

Variables were then systematically removed from the model one-by-one. The variance-inflation factor (VIF) was used to check for multicollinearity among predictors. Lower VIF scores indicate a lower correlation with other predictors. Adjusted R^2, a measure of the predictive power of a model adjusted for the number of predictors in the model, is reported. A higher value indicates that the predictive power of the model is increased based on the predictors in the model (Ratner, 2009). A p-value of less than .05 determined the significance level needed to remain in the model, with adjusted R^2 used to ensure the reduced model retained high predictive value. Final model selection was based on parsimony (i.e., obtaining the simplest model with the highest predictive value).

Statistical Analysis of Baseline Predictors of Change in Tic Severity and Impairment—Linear mixed model repeated measures analysis with backward elimination was performed to evaluate the most relevant baseline variables predictive of change in tic severity and tic impairment from baseline through 11-year follow-up. The model included fixed effects for time (baseline/pre-trial, 10-week/post-CBIT, and 11-year follow-up), predictors, and predictor × time interaction terms. First, baseline predictors were entered together into the model as fixed effects, with dimensional variables centered prior to entry. Models included fixed effects for prior tic treatment effects, including treatment assignment (i.e., CBIT or PST), CGI-I 10-week treatment responder status, and EBT for tics received during the period between post-treatment assessment and long-term follow-up assessment. YGTSS tic severity and YGTSS tic impairment were entered as dependent variables. The model utilized an autoregressive covariance structure of order 1 (which specifies that data from subsequent timepoints are decreasingly correlated with baseline data over time), and maximum likelihood estimation. A random intercept for participant was included, allowing for individual variation in baseline YGTSS tic severity and impairment. Following this procedure, backward elimination was performed as described above to identify the most important predictors. A p-value of less than .05 determined the significance level needed to remain in the model, with Bayesian Information Criterion, a measure of model fit, also used to select the final model. A smaller BIC represents a more optimal balance between model complexity and fit (Neath & Cavanaugh, 2012).

Results

Baseline Predictors of Tic Severity and Tic Impairment at 11-year Follow-up

Tic Severity.—As backward elimination reduced the predictive power (i.e., adjusted R^2) of the model, the full model was selected as optimal. In this full and final model, sex (t = −2.42, p = .018) and parent-reported tic severity (t = 4.75, p < .001) were the most relevant baseline predictors of YGTSS total tic severity in adulthood, controlling for prior treatment effects. Stated differently, female sex and having higher parent-reported tic severity in childhood were associated with greater clinician-rated tic severity in adulthood. No other baseline variables were significant predictors of YGTSS total tic severity in adulthood. This model accounted for 30% of the variance in total tic severity at follow-up (see Table 2).

Tic Impairment.—Sex (t = −2.97, p = .004), stimulant medication status (t = −2.12, p = .038), parent-reported tic severity (t = 2.65, p = .010), and poorer family functioning (t = 2.95, p = .004) in childhood significantly predicted tic impairment in adulthood, controlling for prior tic treatment effects. Taken together, female sex, no stimulant medication use, and having higher parent-reported tic severity and poorer family functioning in childhood were the most relevant predictors of tic impairment in adulthood. There were no other variables within this reduced model. It accounted for 21% of the variance in tic impairment in adulthood, retaining the same predictive value of the full model (see Table 3).

Baseline Predictors of Change in Tic Severity and Tic Impairment through 11-year Follow-up

Tic Severity.—A linear mixed model repeated measures analysis with backward elimination showed that higher baseline parent-reported tic severity (t = 2.67, p = .009), premonitory urge severity (t = 2.18, p = .032, see Table 4), and externalizing symptom severity (t = −2.43, p = .017) were the most important predictors of change in tic severity over time, controlling for prior tic treatment effects. Higher baseline premonitory urge severity and parent-reported tic severity were associated with smaller reductions in tic severity over time, whereas higher externalizing symptom severity was associated with significantly greater reduction in tic severity over time. See Table 4 for the final reduced model. There were no other variables within this final model, and it had the lowest BIC value (1569.05) relative to that (1606.01) of the most complex model, and other more complex models.

Tic Impairment.—Using backward elimination (see Table 5), sex (t = −2.16, p = .034) and externalizing symptoms (t = −2.46, p = .016) were the most important predictors of change in tic impairment from baseline through 11-year follow-up, controlling for prior tic treatment effects. This means that female sex was associated with a smaller reduction in tic impairment over time, and higher externalizing symptoms were associated with greater reduction in impairment over time. The other variables in this model (stimulant medication status, PTQ total, PUTS total, and BFAM-III total) were not statistically significant (see Table 5). This model had a lower BIC value (1715.92) relative to that of the most (1735.11) and least (1784.41) complex models, while having the same two significant predictors as

the least complex model. See supplemental tables 1 and 2 for the full predictor models of change in tic severity and impairment over time.

Discussion

The present study evaluated childhood predictors of tic severity and tic-related impairment in late adolescence and early adulthood, controlling for prior tic treatment effects (i.e., initial treatment assignment, treatment response, and EBT for tics received since the initial trial). Findings showed that female sex and higher parent-reported tic severity in childhood were the most important predictors of higher tic severity in early adulthood. In addition, higher parent-reported tic severity and premonitory urge severity in childhood predicted smaller reductions in tic severity over time, while higher externalizing symptom severity predicted greater reduction in tic severity over time. Further, female sex, higher parent-reported tic severity, absence of stimulant medication, and higher impairment in family functioning were the most important predictors of higher tic impairment in adulthood, whereas female sex predicted a smaller reduction in tic impairment over time, and higher externalizing symptom severity predicted greater reduction in tic impairment over time.

Consistent with our hypotheses and prior research (Garcia-Delgar et al., in press; Lichter & Finnegan, 2015), female sex and higher childhood tic severity each predicted poorer long-term tic outcomes. Indeed, this sex difference is consistent with research showing that the sex ratio for TD exhibits less skew towards male predominance by adulthood (Levine, Szejko, & Bloch, 2019). While cross-sectional studies have shown conflicting sex effects on tic severity in children with TD (Baizabal-Carvallo & Jankovic, in press; Girgis, Martino, & Pringsheim, in press), we found no baseline (i.e., pre-clinical trial) sex differences in tic outcomes in the present sample. Thus, our findings are in line with research showing a less-remitting tic course and greater tic symptom burden and for women with TD in adolescence/adulthood (Garris & Quigg, 2021). Several factors may contribute to present sex differences in adult tic outcomes. Females receive a TD diagnosis at a later average age than males, despite similar age at tic onset between the groups (Santangelo et al., 1994; Schlander, Schwarz, Rothenberger, & Roessner, 2011). Later diagnosis may lead to treatment delays with regard to TD and comorbid conditions, which in turn may delay access to psychoeducation, support, and behavior therapy for TD and co-occurring conditions. Biological differences may also play a role, as suggested by an emerging body of research examining the relationship between sex steroids and TD (Martino, Macerollo, & Leckman, 2013). Preliminary research suggests select women with TD may experience heightened tic severity coinciding with the premenstrual nadir in estrogen (Kompoliti, Goetz, Leurgans, Raman, & Comella, 2001; Martino et al., 2013). Although preliminary, this area of research is ripe for future investigation: future research should examine sex differences in long-term tic course/fluctuation in association with relevant biomarkers.

The significance of higher childhood tic severity as a predictor of long-term tic severity and tic impairment outcomes is supported by several prior studies (Bloch et al., 2006; Cavanna, David, Orth, & Robertson, 2012; Goetz et al., 1992; Groth, Skov, Lange, & Debes, 2019). Although tic severity may decline during adolescence on average, this may be temporary in many cases, as tics have been shown to reemerge in adulthood for many individuals

(Schaefer, Chow, Louis, & Robakis, 2017). Thus, childhood tic severity may serve as an important early clinical indicator of long-term tic outcomes. This finding speaks to the need for continued behavioral and supportive treatments across adolescence and adulthood to manage tic symptom exacerbations and improve quality of life, particularly for those exhibiting high tic severity in youth. Results also suggest tic interventions administered even earlier in childhood (e.g., CBIT-JR; Bennett et al., 2020) may improve long-term outcomes – a hypothesis certainly worth testing.

Childhood premonitory urge severity uniquely predicted a smaller reduction in tic severity over time, as it was not predictive of other long-term outcomes. This finding aligned with our hypothesis. It is possible that higher premonitory urge severity may interfere with the patient's ability to block or suppress tics. This finding has implications for the application of interventions that directly target one's relationship with the premonitory urge. For example, third-wave behavior therapies (e.g., mindfulness-based stress reduction, and acceptance and commitment therapy-enhanced habit reversal training) centered on mindfulness and non-judgmental, present-focused awareness of premonitory urges, without performing the tic or exerting efforts to control urges (Franklin, Best, Wilson, Lowe, & Compton, 2011; Reese et al., 2015), may decrease the tendency to react to one's own premonitory urges.

Being off stimulant medication, and having poorer family functioning predicted higher tic impairment in adulthood. There is research to suggest that stimulant medication use in youth with ADHD diminishes the structural and functional neural alterations characteristic of medication-free ADHD patients (Spencer et al., 2013). Future research is needed to determine whether stimulant medication use provides any such neuroprotective effect in TD. With respect to family functioning, TD may contribute to family tension, marital problems, parental burden, patient and family isolation, and family economic strain (Ludlow, Brown, & Schulz, 2016; O'Hare et al., 2017; Vermilion et al., 2020). Conversely, a negative family environment may lead to more negative family responses to child tics and worsening tic course, irrespective of initial tic severity. This could have a lasting adverse impact on individuals with TD into adulthood, and suggests the importance of direct assessment and treatment of family problems during childhood to improve positive communication and reduce stigma (Malli, Forrester-Jones, & Triantafyllopoulou, 2019). CBIT provides some family intervention through function-based assessment and intervention and inclusion of a parent or caregiver as a support person in habit reversal training (HRT; Woods et al., 2008). However, more targeted treatment may be needed to address broader family impairment. One such behavioral intervention, Living with Tics (McGuire et al., 2015), provides family intervention in addition to HRT. Beyond providing function-based assessment and intervention, this treatment offers training to families in differentiating between tic and non-tic behaviors, increasing parental support through support group meetings and self-care activities, and assisting with coordination of medical visits to ease burden (Himle, Wellen, & Hayes, 2018).

Externalizing symptom (i.e., CBCL rule breaking and aggressive behavior scales) severity during childhood predicted both greater reduction in tic severity and tic impairment over time. It is worth noting that the CBCL externalizing items do not include ADHD symptoms. Although counterintuitive, one potential explanation for this pattern of findings could be that

as initially-high externalizing behaviors (oppositional defiant disorder, rage attacks, conduct problems, other disruptive behaviors) in select youth with TD (Sukhodolsky et al., 2003) improve with age, their impact on tic symptoms may diminish with the development of self-regulatory skills, resulting in improved long-term tic outcomes. One study showed that improvements in tic severity over a one-year period were associated with improvements in response inhibition performance over time (Yaniv, Benaroya-Milshtein, Steinberg, Ruhrman, Apter, & Lavidor, 2018), suggesting this self-regulatory skill is related to symptom course. An alternative explanation could be that externalizing symptoms, which predict more frequent and longer duration mental health service utilization among children seen in mental health agencies (Reid et al., 2019), may have led to increased service use in the current sample in the years following the initial trial. Services obtained for co-occurring symptoms may have indirectly improved tics. Our analysis controlled for explicit EBT for tics during the follow-up period but not EBT for comorbidity.

The present study has some limitations of note. A selection bias may have occurred, whereby individuals who elected to partake in our long-term follow-up may differ in important ways from individuals lost to follow-up. However, the baseline characteristics for the follow-up sample (see Table 1) suggest these participants are clinically representative of the full sample from the original clinical trial of behavior therapy for tics in youth (Piacentini et al., 2010). As this is a treatment-seeking sample stemming from a clinical trial, findings may not generalize to individuals who have not received treatment. Also, the relatively small sample sizes for certain variables (e.g., female sex, and stimulant medication use in childhood) may limit the ability to draw conclusions from these findings regarding the broader TD population. However, the male-to-female ratio of 4:1 in the present sample is in line with the commonly observed sex ratio for child samples (Freeman et al., 2000). Further, the follow-up sample is comparable to that of other large treatment-seeking samples. The current sample exhibits similar baseline tic severity (i.e., moderate to severe; Andrén et al., 2021; Coffey et al., 2000), a somewhat higher rate (37%) of baseline tic medication use (Andrén et al., 2021; Groth et al., 2017), and a similar-to-somewhat-lower rate (60%) of psychiatric comorbidity (Coffey et al., 2000; Freeman et al., 2000; Hirschtritt et al., 2015) to other treatment-seeking TD samples, suggesting the sample is clinically representative of clinical samples of TD patients. Additionally, our measure of tic severity at baseline is a parent-reported scale, whereas the Yale Global Tic Severity, the dependent variable, is a gold-standard clinician-rated interview. However, this decision was made for statistical purposes, as outlined in the statistical analysis section. Further, although we controlled for EBT for tics received during the follow-up period, we lack detail regarding the duration, and quality of these interventions. Moreover, although our sample is clinically well-characterized, with psychiatric diagnoses obtained via interview, we did not include specific psychiatric diagnoses as baseline predictors. This precludes our ability to draw conclusions regarding the importance of specific disorders (e.g., ADHD, OCD) commonly comorbid with TD. However, our use of dimensional internalizing and externalizing symptom severity ratings is consistent with support for dimensional over categorical approaches to psychopathology (Hengartner & Lehmann, 2017).

In conclusion, the present study evaluated childhood predictors of tic severity and tic-related impairment at 11-year CBIT follow-up and their change over time, controlling for prior

treatment effects. Notably, this statistical control for prior tic treatment effects should not be interpreted as indicative of an inability to alter the trajectory of long-term tic outcomes with intervention. Rather, it accounts for the receipt of prior treatment for tics in order to better identify key clinical characteristics, which predict long-term tic outcomes above and beyond those already accounted for by effects of prior tic treatment. Indeed, our findings revealed various predictors of long-term outcomes, with female sex and childhood tic severity being important predictors for both long-term tic severity and impairment, being off stimulant medication and family impairment predicting higher tic impairment in adulthood, premonitory urge severity predicting a smaller reduction in tic severity over time, and externalizing symptoms predicting greater reduction in tic severity and impairment over time. Findings have implications for providing patients, parents, and clinicians with guidance regarding prognosis among youth with TD. Results suggest the importance of providing early and/or targeted interventions to positively influence symptom trajectory in susceptible youth with TD. Future studies should seek to identify the genetic and neural predictors of long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Christopher C. Bauer, M.S., Silvia Orellana, B.S., Madeline Rasch, M.S., and Caitlin Lau, M.S.

Declaration of Interest

Dr. Ricketts has received honoraria and funding from the Tourette Association of America (TAA), and serves on their Diversity Committee. She has also received research funding from the National Institute of Mental Health (NIMH), and TLC Foundation for Body-Focused Repetitive Behaviors (BFRBs): BFRB Precision Medicine Initiative. She has received honoraria from the Centers for Disease Control and Prevention and Springer Nature. Dr. Woods receives royalties from Guilford Press, Springer Press, and Oxford University Press. Dr. Woods also receives speaking fees from the Tourette Association of America. Dr. Espil receives research support from the Foundation for OCD Research and past support from the TAA and the American Academy of Neurology (AAN). Dr. McGuire has received support from the TAA, AAN, the Brain Research Foundation, American Psychological Foundation, and the Hilda and Preston Davis Family Foundation. He receives royalties from Elsevier, and serves as a consultant for Signant Health, Syneos Health, and Luminopia. Mr. Stiede and Ms. Schild have no competing financial interests or personal relationships to declare. Dr. Yadegar has received honorarium from Springer Nature. Dr. Bennett has received research support, speaking fees and travel support for speaking engagements from the TAA. Dr. Bennett also receives royalties from Wolters Kluwer. Dr. Specht receives research support and speaking honoraria from the TAA. Dr. Chang has reported no financial interests or potential conflicts of interest. Dr. Scahill receives research support from the National Institutes of Health and Department of Defense. He also serves as a consultant for Roche, Impel, and Janssen. He also receives royalties from Oxford, Guilford, and the American Psychological Association and licensing royalties for the Parent-rated Anxiety Scale-ASD. Dr. Wilhelm is a presenter for the Massachusetts General Hospital Psychiatry Academy in educational programs supported through independent medical education grants from pharmaceutical companies; she has received royalties from Elsevier Publications, Guilford Publications, New Harbinger Publications, Springer, and Oxford University Press. Dr. Wilhelm has also received speaking honoraria from various academic institutions and foundations, including the International OCD Foundation, TAA, and Brattleboro Retreat. In addition, Dr. Wilhelm received payment from the Association for Behavioral and Cognitive Therapies for her role as Associate Editor for the Behavior Therapy journal, as well as from John Wiley & Sons, Inc. for her role as Associate Editor on the journal Depression & Anxiety. Dr. Wilhelm has also received honorarium from One-Mind for her role in PsyberGuide Scientific Advisory Board. Dr. Wilhelm has received salary support from Novartis and Telefonica Alpha, Inc. Dr. Peterson reports receiving royalties from Oxford University Press for treatment manuals on tic disorders and receiving honoraria for CME presentations from the TAA. Dr. Walkup serves on the advisory board and Speaker's Bureau of the TAA and receives royalties from Oxford University Press, and Wolters Kluwer. Dr. Piacentini receives research support from NIMH, the TLC Foundation for BFRBs, and Pfizer Pharmaceuticals; publication royalties from Guilford Press and

Oxford University Press; and travel/speaking honoraria from the TAA, International OCD Foundation, and the TLC Foundation for BFRBs.

This research was conducted with research support from the Tourette Association of America funding to Drs. Espil, Specht, Chang, Walkup, Piacentini, and Woods, and National Institutes of Mental Health (NIMH) R01MH070802 funding to Dr. Piacentini, and prepared with research support from NIMH K23MH113884 funding to Dr. Ricketts. The content is the responsibility of the authors and is not necessarily representative of the views of the Tourette Association of America or the National Institutes of Health.

References

Achenbach TM, & Rescorla L (2001). Manual for the ASEBA school-age forms & profiles: An integrated system of multi-informant assessment. ASEBA.

Albores-Gallo L, Lara-Muñoz C, Esperón-Vargas C, Zetina JA, Soriano AM, & Colin GV (2007). Validity and reliability of the CBCL/6–18. Includes DSM scales. Actas Espanolas de Psiquiatria, 35, 393–399. [PubMed: 18004676]

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). 10.1176/appi.books.9780890425596

Andrén P, Wachtmeister V, Franze J, Speiner C, de la Cruz LF, Andersson E, de Schipper E, Rautio D, Silverberg-Mörse M, Serlachius E, & Mataix-Cols D (2021). Effectiveness of behavior therapy for children and adolescents with Tourette syndrome and chronic tic disorder in a naturalistic setting. Child Psychiatry & Human Development, 52, 739–750. 10.1007/s10578-020-01098-y [PubMed: 33315190]

Baizabal-Carvallo JF, & Jankovic J (in press). Sex differences in patients with Tourette syndrome. CNS Spectrums, 1–7. 10.1017/S1092852922000074

Bennett SM, Capriotti M, Bauer C, Chang S, Keller AE, Walkup J, Woods DW, & Piacentini J (2020). Development and open trial of a psychosocial intervention for young children with chronic tics: The CBIT-JR study. Behavior Therapy, 51, 659–669. 10.1016/j.beth.2019.10.004 [PubMed: 32586437]

Bloch MH, & Leckman JF (2009). Clinical course of Tourette Syndrome. Journal of Psychosomatic Research, 67, 497–501. 10.1016/j.jpsychores.2009.09.002 [PubMed: 19913654]

Bloch MH, Peterson BS, Scahill L, Otka J, Katsovich L, Zhang H, & Leckman JF (2006). Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Archives of Pediatric Adolescent Medicine, 160, 65–69. 10.1001/archpedi.160.1.65

Burd L, Kerbeshian PJ, Barth A, Klug MG, Avery PK, & Benz B (2001). Long-term follow-up of an epidemiologically defined cohort of patients with Tourette syndrome. Journal of Child Neurology, 16, 431–437. 10.1177/088307380101600609 [PubMed: 11417610]

Byler DL, Chan L, Lehman E, Brown AD, Ahmad S, & Berlin C (2015). Tourette syndrome: A general pediatrician's 35-year experience at a single center with follow-up in adulthood. Clinical Pediatrics, 54, 138–144. 10.1177/0009922814550396 [PubMed: 25200367]

Cavanna AE, David K, Orth M, & Robertson MM (2012). Predictors during childhood of future health-related quality of life in adults with Gilles de la Tourette syndrome. European Journal of Paediatric Neurology, 16, 605–612. 10.1016/j.ejpn.2012.02.004 [PubMed: 22381812]

Chang S, Himle MB, Tucker BTP, Woods DW, & Piacentini J (2009). Initial psychometric properties of a brief parent-report instrument for assessing tic severity in children with chronic tic disorders. Child & Family Behavior Therapy, 31, 181–191. 10.1080/07317100903099100

Coffey BJ, Biederman J, Smoller JW, Geller DA, Sarin P, Schwartz S, & Kim GS (2000). Anxiety disorders and tic severity in juveniles with Tourette's disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 39, 562–568. 10.1097/00004583-200005000-00009 [PubMed: 10802973]

Conelea CA, Woods DW, Zinner SH, Budman C, Murphy T, Scahill LD, Compton SN, & Walkup J (2011). Exploring the impact of chronic tic disorders on youth: Results from the Tourette Syndrome Impact Survey. Child Psychiatry and Human Development, 42, 219–242. 10.1007/s10578-010-0211-4 [PubMed: 21046225]

Edwards KR, Mendlowitz S, Jackson E, Champigny C, Specht M, Arnold P, Gorman D, & Dimitropoulos G (2017). A qualitative exploration of the experiences of children and adolescents

with Tourette syndrome. Journal of the Canadian Academy of Child and Adolescent Psychiatry, 26, 39–44. [PubMed: 28331502]

Erenberg G, Cruse RP, & Rothner AD (1987). The natural history of Tourette syndrome: A follow-up study. Annals of Neurology, 22, 383–385. 10.1002/ana.410220317 [PubMed: 3479043]

Espil FM, Woods DW, Specht MW, Bennett SM, Walkup JT, Ricketts EJ, McGuire JF, Stiede JT, Schild JS, Chang SW, Peterson AL, Scahill L, Wilhelm S, & Piacentini J (2022). Long-term outcomes of behavior therapy for youth with Tourette disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 10.1016/j.jaac.2021.08.02

Ferdinand RF (2008). Validity of the CBCL/YSR DSM-IV scales anxiety problems and affective problems. Journal of Anxiety Disorders, 22, 126–134. 10.1016/j.janxdis.2007.01.008 [PubMed: 17321103]

Franklin ME, Best SH, Wilson MA, Loew B, & Compton SN (2011). Habit reversal training and Acceptance and Commitment Therapy for Tourette syndrome: A pilot project. Journal of Developmental and Physical Disabilities, 23, 49–60. 10.1007/s10882-010-9221-1

Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, & Sandor P (2000). An international perspective on Tourette syndrome: Selected findings from 3500 individuals in 22 countries. Developmental Medicine and Child Neurology, 42, 436–447. 10.1017/s0012162200000839 [PubMed: 10972415]

Garcia-Delgar B, Servera M, Coffey BJ, Lazaro L, Openneer T, Benaroya-Milshtein N, Hoekstra PJ, Dietrich A, Morer A on behalf of the EMTICS collaborative group. (2021). Tic disorders in children and adolescents: Does the clinical presentation differ in males and females? A report by EMTICS group. European Child & Adolescent Psychiatry. 10.1007/s00787-021-01751-4

Gardner DL, Huber CH, Steiner R, Vazquez LA, & Savage TA (2008). The development and validation of the inventory of family protective factors: A brief assessment for family counseling. The Family Journal, 16, 107–117. 10.1177/1066480708314259

Garris J, & Quigg M (2021). The female patient: Sex differences in Tourette disorder. Neuroscience and Biobehavioral Reviews, 129, 261–268. 10.1016/j.neubiorev.2021.08.001 [PubMed: 34364945]

Girgis J, Martino D, Pringsheim T (2022). Influence of sex on tic severity and psychiatric comorbidity profile in patients with pediatric tic disorder. Developmental Medicine & Child Neurology, 64, 488–494. 10.1111/dmcn.15088 [PubMed: 34672366]

Goetz CG, Tanner CM, Stebbins GT, Leipzig G, & Carr WC (1992). Adult tics in Gilles de la Tourette's syndrome. Neurology, 42, 784–788. 10.1212/wnl.42.4.784 [PubMed: 1565232]

Groth C, Debes NM, Rask CU, Lange T, & Skov L (2017). Course of Tourette syndrome and comorbidities in a large prospective clinical study. Journal of the American Academy of Child & Adolescent Psychiatry, 56, 304–312. 10.1016/j.jaac.2017.01.010 [PubMed: 28335874]

Groth C, Skov L, Lange T, & Debes NM (2019). Predictors of the clinical course of Tourette syndrome: A longitudinal study. Journal of Child Neurology, 34, 913–921. 10.1177/088307381986724 [PubMed: 31411102]

Hengartner MP, & Lehmann SN (2017). Why psychiatric research must abandon traditional diagnostic classification and adopt a fully dimensional scope: Two solutions to a persistent problem. Frontiers in Psychiatry, 8, 101. 10.3389/fpsyt.2017.00101 [PubMed: 28638352]

Himle MB, Wellen BCM, & Hayes LP (2018). Chapter 14 – Family issues associated with tics. The clinician's guide to treatment and management of youth with Tourette syndrome and tic disorders. Academic Press. 10.1016/B978-0-12-811980-8.00014-5

Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, King RA, Sandor P, McMahon WM, Lyon GJ, Cath DC, Kurlan R, Robertson MM, Osiecki L, Scharf JM, Mathews CA, & Tourette Syndrome Association International Consortium for Genetics. (2015). Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry, 72, 325–333. 10.1001/jamapsychiatry.2014.2650 [PubMed: 25671412]

Kompoliti K, Goetz CG, Leurgans GS, Raman R, & Comella CL (2001). Estrogen, progesterone, and tic severity in women with Gilles de la Tourette syndrome. Neurology, 57, 1519. 10.1212/wnl.57.8.1519

Leckman JF, Zhang H., Vitale A, Lahnin F, Lynch K, Bondi C, Kim YS, & Peterson BS (1998). Course of tic severity in Tourette Syndrome: The first two decades. Pediatrics, 102, 14–19. 10.1542/peds.102.1.14 [PubMed: 9651407]

Leckman JF, King RA, & Bloch MH (2014). Clinical features of Tourette syndrome and tic disorders. Journal of Obsessive-Compulsive and Related Disorders, 3, 372–379. 10.1016/j.jocrd.2014.03.004 [PubMed: 30197854]

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, & Cohen DJ (1989). The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity. Journal of the American Academy of Child & Adolescent Psychiatry, 28, 566–573. 10.1016/j.jocrd.2014.03.004 [PubMed: 2768151]

Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, Kim Y-S, & Peterson BS (1998). Course of tic severity in Tourette syndrome: The first two decades. 102, 14–19. 10.1542/peds.102.1.14

Leung PW, Kwong SL, Tang CP, Ho TP, Hung SF, Lee CC, Hong SL, Chiu CM, & Liu WS (2006). Test-retest reliability and criterion validity of the Chinese version of CBCL, TRF, and YSR. Journal of Child Psychology and Psychiatry, 47, 970–973. 10.1111/j.1469-7610.2005.01570.x [PubMed: 16930392]

Levine JLS, Szejko N, & Bloch MH (2019). Meta-analysis: Adulthood prevalence of Tourette syndrome. Progress in Neuro-psychopharmacology & Biological Psychiatry, 95, 109675. 10.1016/j.pnpbp.2019.109675 [PubMed: 31220521]

Lichter DG, & Finnegan SG (2015). Influence of gender on Tourette syndrome beyond adolescence. European Psychiatry, 30, 334–340. 10.1016/j.eurpsy.2014.07.00 [PubMed: 25193042]

Lowe TL, Capriotti MR, & McBurnett K (2019). Long-term follow-up of patients with Tourette's syndrome. Movement Disorders Clinical Practice, 6, 40–45. 10.1002/mdc3.12696 [PubMed: 30746414]

Ludlow AK, Brown R, & Schulz J (2016). A qualitative exploration of the daily experiences and challenges faced by parents and caregivers of children with Tourette's syndrome. Journal of Health Psychology, 23, 1790–1799. 10.1177/1359105316669878 [PubMed: 27682339]

Lyneham HJ, Abbott MJ, & Rapee RM (2007). Interrater reliability of the anxiety disorders interview schedule for DSM-IV: Child and parent version. Journal of the American Academy of Child and Adolescent Psychiatry, 46, 731–736. 10.1097/chi.0b013e3180465a09 [PubMed: 17513985]

Malli MA, Forrester-Jones R, & Triantafyllopoulou P (2019). "Tourette's is a lonely place": An interpretative phenomenological analysis of the personal experience and identity of adults with Tourette's syndrome. Journal of Developmental and Physical Disabilities, 31, 819–845. 10.1007/s10882-019-09676-2

Martino D, Macerollo A, & Leckman JF (2013). Neuroendocrine aspects of Tourette syndrome. International Review of Neurobiology, 112, 239–279. 10.1016/B978-0-12-411546-0.00009-3 [PubMed: 24295624]

McGuire JF, Arnold E, Park JM, Nadeau JM, Lewin AB, Murphy TK, & Storch EA (2015). Living with tics: Reduced impairment and improved quality of life for youth with chronic tic disorders. Psychiatry Research, 225, 571–579. 10.1016/j.psychres.2014.11.045 [PubMed: 25500348]

McGuire JF, Piacentini J, Storch EA, Murphy TK, Ricketts EJ, Woods DW, Walkup JT, Peterson AL, Wilhelm S, Lewin AB, McCracken JT, Leckman JF, & Scahill L (2018). A multicenter examination and strategic revisions of the Yale Global Tic Severity Scale. Neurology, 90, e1711–e1719. 10.1212/WNL.0000000000005474 [PubMed: 29653992]

Neath AA, & Cavanaugh JE (2012). The Bayesian information criterion: Background, derivation and applications. WIREs Computational Statistics, 4, 199–203. 10.1002/wics.199

O'Hare D, Eapen V, Grove R, Helmes E, McBain K, & Reece J (2017). Youth with Tourette syndrome: Parental perceptions and experiences in the Australian context. Australian Journal of Psychology, 69, 48–57. 10.1111/ajpy.12111

Openneer TJC, Tárnok Z, Bognar E, Benarova-Milshtein N, Garcia-Delgar B, Morer A, Steinberg T, Hoekstra PJ, Dietrich A, and the EMTICS collaborative group (2020). The Premonitory Urge for Tics Scale in a large sample of children and adolescents: Psychometric properties in a developmental context. An EMTICS study. European Child & Adolescent Psychiatry, 29, 1411–1424. 10.1007/s00787-019-01450-1 [PubMed: 31802271]

Pappert EJ, Goetz CG, Louis ED, Blasucci L, & Leurgans S (2003). Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology, 61, 936–940. 10.1212/01.wnl.0000086370.10186.7c [PubMed: 14557563]

Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, Ginsburg S, Deckersbach T, Dziura J, Levi-Pearl S, & Walkup JT (2010). Behavior therapy for children with Tourette disorder: A randomized controlled trial. JAMA, 303, 1929–1937. 10.1001/jama.2010.607 [PubMed: 20483969]

Pringsheim T, Okun MS, Muller-Vahl K, Martino D, Jankovic J, Cavanna AE, Woods DW, Robinson M, Jarvie E, Roessner V, Oskoui M, Holler-Managan Y, & Piacentini J (2019). Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology, 92, 896–906. 10.1212/WNL.0000000000007466 [PubMed: 31061208]

Raines JM, Edwards KR, Sherman MF, Higginson CI, Winnick JB, Navin K, Gettings JM, Conteh F, Bennett SM, & Specht MW (2017). Premonitory Urges for Tics Scale (PUTS): Replication and extension of psychometric properties in youth with chronic tic disorders (CTDs). Journal of Neural Transmission, 125, 727–734. 10.1007/s00702-017-1818-4 [PubMed: 29185077]

Ratner B (2009). The correlation coefficient: Its values range between +1/−1, or do they? Journal of Targeting, Measurement and Analysis for Marketing, 17, 139–142. 10.1057/jt.2009.5

Reese HE, Vallejo Z, Rasmussen J, Crowe K, Rosenfield E, & Wilhelm S (2015). Mindfulness-based stress reduction for Tourette syndrome and chronic tic disorder: A pilot study. Journal of Psychosomatic Research, 78, 293–298. https://doi.org/0.1016/j.jpsychores.2014.08.001 [PubMed: 25149879]

Reid GJ, Stewart SL, Barwick M, Carter J, Leschied A, Neufeld RWJ, Pierre JS, Tobon JI, Vingilis E, & Zaric GS (2019). Predicting patterns of service utilization within children's mental health agencies. BMC Health Services Research, 19, 993. [PubMed: 31870372]

Ricketts EJ, Bauer CC, Ran D, Himle MB, & Woods DW (2016). Pilot open case series of voice over internet protocol-delivered assessment and behavior therapy for chronic tic disorders. Cognitive and Behavioral Practice, 23, 40–50. 10.1016/j.cbpra.2014.09.003 [PubMed: 30595642]

Ricketts EJ, McGuire JF, Chang S, Bose D, Rasch MM, Woods DW, Specht MW, Walkup JT, Scahill L, Wilhelm S, Peterson AL, & Piacentini J (2018). Benchmarking treatment response in Tourette's disorder: A psychometric evaluation and signal detection analysis of the Parent Tic Questionnaire. Behavior Therapy, 49, 46–56. 10.1016/j.beth.2017.05.006 [PubMed: 29405921]

Santangelo SL, Pauls DL, Goldstein JM, Faraone SV, Tsuang MT, & Leckman JF (1994). Tourette's syndrome: What are the influences of gender and comorbid obsessive-compulsive disorder? Journal of the American Academy of Child & Adolescent Psychiatry, 33, 795–804. 10.1097/00004583-199407000-00004 [PubMed: 8083136]

Schaefer SM, Chow CA, Louis ED, & Robakis D (2017). Tic exacerbation in adults with Tourette syndrome. Tremor and Other Hyperkinetic Movements, 7, 450. 10.7916/D8FF3Z1Q [PubMed: 28289551]

Schlander M, Schwarz O, Rothenberger A, & Roessner V (2011). Tic disorders: Administrative prevalence and co-occurrence with attention-deficit/hyperactivity disorder in a German community sample. European Psychiatry, 26, 370–374. 10.1016/j.eurpsy.2009.10.003 [PubMed: 20427154]

Silverman WK, & Albano AM (1996). The Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent Versions. The Psychological Corporation.

Silverman WK, Saavedra LM, & Pina AA (2001). Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: Child and parent versions. Journal of the American Academy of Child and Adolescent Psychiatry, 40, 937–944. 10.1097/00004583-200108000-00016 [PubMed: 11501694]

Skinner HA, Steinhauer PD, & Santa-Barbara J (1995). Family Assessment Measure version III: Technical manual. Multi-Health Systems.

Skinner HA, Steinhauer P, & Sitarenios G (2000). Family Assessment Measure (FAM) and process of model of family functioning. Journal of Family Therapy, 22, 190–210. 10.1111/1467-6427.00146

Spencer TJ, Brown A, Seidman LJ, Valera EM, Makris N, Lomedico A, Faraone SV, & Biederman J (2013). Effect of psychostimulants on brain structure and function in ADHD: A qualitative

review of MRI-based neuroimaging studies. Journal of Clinical Psychiatry, 74, 902–917. 10.4088/JCP.12r08287 [PubMed: 24107764]

Storch EA, Murphy TK, Geffken GR, Sajid M, Allen P, Roberti JW, & Goodman WK (2005). Reliability and validity of the Yale Global Tic Severity Scale. Psychological Assessment, 17, 486–491. 10.1037/1040-3590.17.4.486 [PubMed: 16393016]

Sukhodolsky DG, Scahill L, Zhang H, Peterson BS, King RA, Lombroso PJ, Katsovich L, Findley D, & Leckman JF (2003). Disruptive behavior in children with Tourette's syndrome: Association with ADHD comorbidity, tic severity, and functional impairment. Journal of the American Academy of Child and Adolescent Psychiatry, 42, 98–105. 10.1097/00004583-200301000-00016 [PubMed: 12500082]

Thériault MG, Bécue J, Lespérance P, Chouinard S, Rouleau G, & Richer F (2018). Oppositional behavior and longitudinal predictions of early adulthood mental health problems in chronic tic disorders. Psychiatry Research, 266, 301–318. 10.1016/j.psychres.2018.03.026 [PubMed: 29576412]

Vermilion J, Augustine E, Adams HR, Vierhile A, Lewin AB, Thatcher A, McDermott MP, O'Connor T, Kurlan R, van Wijngaarden E, Murphy TK, & Mink JW (2020). Tic disorders are associated with lower child and parent quality of life and worse family functioning. Pediatric Neurology, 105, 48–54. 10.1016/j.pediatrneurol.2019.12.003 [PubMed: 32029331]

Wood JJ, Piacentini JC, Bergman RL, McCracken J, & Barrios V (2002). Concurrent validity of the anxiety disorders section of the Anxiety Disorders Interview Schedule for DSM-IV: Child and parent versions. Journal of Clinical Child and Adolescent Psychology, 31, 335–342. 10.1207/S15374424JCCP3103_05 [PubMed: 12149971]

Woods DW, Piacentini J, Himle MB, & Chang S (2005). Premonitory Urge for Tics Scale (PUTS): Initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. Journal of Developmental & Behavioral Pediatrics, 26, 397–403. 10.1097/00004703-200512000-00001 [PubMed: 16344654]

Woods DW, Piacentini J, Change SW, Deckersbach T Ginsburg GS, Peterson AL, Scahill LD, Walkup JT, & Wilhelm S (2008). Managing Tourette syndrome. A behavioral intervention for children and adults. Therapist Guide. Oxford University Press. 10.1093/med:psych/9780195341287.001.0001

Yaniv A, Benaroya-Milshtein N, Steinberg T, Ruhrman D, Apter A, & Lavidor M (2018). Executive control development in Tourette syndrome and its role in tic reduction. Psychiatry Research, 262, 527–535. 10.1016/j.psychres.2017.09.038 [PubMed: 28965812]

Table 1

Baseline Characteristics for Follow-up Sample and full CBIT Sample

Characteristic	Follow-up Sample (n = 80)	Full CBIT Sample (n = 126)
Age M (SD)	11.47 (2.42)	11.73 (2.32)
Male n (%)	60 (75.0%)	99 (78.5%)
On Tic Med n (%)	29 (36.3%)	46 (36.5%)
On Stimulant Med n (%)	9 (11.3%)	12 (9.5%)
Any Comorbid Psychiatric Diagnosis n (%)	47 (58.8%)	81 (64.3%)
Any Attention-Deficit/Hyperactivity Disorder n (%)	19 (23.8%)	33 (26.2%)
Oppositional Defiant Disorder n (%)	5 (6.3%)	9 (7.1%)
Any Anxiety Disorder n (%)	28 (35.0%)	46 (36.5%)
YGTSS Total Tic Severity M (SD)	24.82 (5.88)	24.66 (6.06)
YGTSS Impairment M (SD)	23.65 (8.25)	23.65 (8.42)
Parent Tic Questionnaire M (SD)	37.24 (20.06)	36.11 (20.55)
Premonitory Urge for Tics Scale Total M (SD)	17.16 (6.72)	17.36 (6.58)
CBCL Internalizing T Score M (SD)	52.44 (11.72)	53.55 (11.33)
CBCL Externalizing T Score M (SD)	47.25 (10.30)	48.96 (10.38)
BFAM-III Total Score M (SD)	24.80 (4.86)	26.07 (5.79)

Note. CBIT = Comprehensive Behavioral Intervention for Tics; YGTSS = Yale Global Tic Severity Scale; CBCL = Achenbach; Child Behavior Checklist 6/18; B-FAM-III = Brief-Family Assessment Measure-III.

Table 2

Multiple Linear Regression analysis to identify baseline predictors of YGTSS Total Tic Severity at 11-year follow-up

Full and Final Model							
Predictor	***B***	**SE**	***β***	***t***	***p***	**VIF**	**Adj. R^2**
							.30
Constant	22.03	4.18		5.27	<.001		
Treatment Assignment	−0.77	2.20	−.04	−0.35	.728	1.43	
CGI-I 10-week Tx. Responder Status	−0.55	2.30	−.03	−0.24	.813	1.41	
Evidence-based Tx. for Tics	−0.96	2.01	−.05	−0.48	.635	1.14	
Sex	**−5.52**	**2.28**	**−.25**	**−2.42**	**.018**	**1.16**	
Tic Medication Status	2.09	2.20	.11	0.95	.347	1.34	
Stimulant Medication Status	−4.91	2.96	−.16	−1.66	.102	1.04	
PTQ Total	**0.27**	**.06**	**.57**	**4.75**	**<.001**	**1.54**	
PUTS Total	0.29	.15	.20	1.89	.063	1.21	
CBCL Internalizing Total	−0.04	.11	−.06	−0.41	.680	1.86	
CBCL Externalizing Total	−0.09	.12	−.10	−0.79	.434	1.79	
B-FAM-III Total	0.40	.20	.21	1.98	.052	1.15	

Note. YGTSS = Yale Global Tic Severity Scale; PTQ = Parent Tic Questionnaire; PUTS = Premonitory Urge for Tics Scale; CBCL = Achenbach Child Behavior Checklist 6/18; B-FAM-III = Brief-Family Assessment Measure-III.

Table 3

Multiple Linear Regression analysis to identify baseline predictors of YGTSS Impairment at 11-year follow-up

Full Model							
Predictor	***B***	**SE**	***β***	***t***	***p***	**VIF**	**Adj. R^2**
							.21
Constant	17.41	5.01		3.47	<.001		
Treatment Assignment	−0.11	2.63	−.01	−0.04	.967	1.43	
CGI-I 10-week Tx. Responder Status	2.72	2.76	.12	0.99	.327	1.41	
Evidence-Based Tx. for Tics	−2.99	2.41	−.14	−1.24	.220	1.14	
Sex	**−8.72**	**2.73**	**−.35**	**−3.19**	**.002**	**1.16**	
Tic Medication Status	2.55	2.64	.11	0.97	.338	1.34	
Stimulant Medication Status	−6.79	3.54	−.20	−1.92	.060	1.04	
PTQ Total	**0.17**	**0.07**	**.32**	**2.50**	**.015**	**1.54**	
PUTS Total	0.27	0.18	.17	1.51	.135	1.21	
CBCL Internalizing Total	−0.04	0.13	−.04	−0.28	.783	1.86	
CBCL Externalizing Total	−0.13	0.14	−.12	−0.90	.374	1.79	
B-FAM-III Total	**0.72**	**0.24**	**.33**	**2.97**	**.004**	**1.15**	
Final Reduced Model							
Predictor	***B***	**SE**	***β***	***t***	***p***	**VIF**	**Adj. R^2**
							.21
Constant	15.94	4.75		3.36	.001		
Treatment Assignment	1.52	2.49	.07	0.61	.545	1.28	
CGI-I 10-week Tx. Responder Status	2.92	2.73	.13	1.07	.289	1.38	
Evidence-Based Tx. for Tics	−3.98	2.35	−.18	−1.69	.095	1.08	
Sex	**−8.00**	**2.69**	**−.32**	**−2.97**	**.004**	**1.12**	
Stimulant Medication	**−7.46**	**3.52**	**−.22**	**−2.12**	**.038**	**1.02**	
PTQ Total	**0.16**	**0.06**	**.29**	**2.65**	**.010**	**1.12**	
B-FAM-III Total	**0.69**	**0.23**	**.31**	**2.95**	**.004**	**1.05**	

Note. YGTSS = Yale Global Tic Severity Scale; PTQ = Parent Tic Questionnaire; PUTS = Premonitory Urge for Tics Scale; CBCL = Achenbach Child Behavior Checklist 6/18; B-FAM-III = Brief-Family Assessment Measure-III.

Table 4

Linear mixed model repeated measures analysis to identify predictors of change in YGTSS Total Tic Severity from baseline through 11-year follow-up: Reduced Model

YGTSS Total										
	Estimates of Fixed Effects					**Estimates of Covariance Parameters**				
	Estimate (SE)	**df**	***t***	***p***	**95% CI**		**Estimate (SE)**	**Wald Z**	***p***	**95% CI**
Intercept	26.65 (2.20)	80.83	12.10	<.001	22.27 – 31.03	Repeated Measures AR1 diagonal	33.48 (4.41)	7.59	<.001	25.87 – 43.35
Time	−4.56 (0.47)	86.03	−9.78	<.001	−5.49 – −3.63	AR1 rho	−0.12 (0.14)	−0.86	.390	−0.39 – 0.16
Treatment Assignment	0.20 (1.24)	74.11	0.16	.872	−2.24 – 2.64	Intercept Variance	9.84 (4.10)	2.40	.016	4.35 – 22.25
TX Responder Status	−3.88 (1.24)	74.17	−3.17	.003	−6.35 – −1.41					
Evidence-Based Tic TX	−1.98 (1.09)	74.57	−1.82	.073	−4.14 – 0.19					
PTQ Total	0.12 (0.04)	150.06	3.35	.001	0.05 – 0.19					
PTQ × Time	**0.05 (0.02)**	**86.03**	**2.18**	**.032**	**0.05 – 0.10**					
PUTS Total	−0.11 (0.11)	152.50	−1.02	.311	−0.32 – 0.10					
PUTS Total × Time	**0.19 (0.07)**	**86.03**	**2.67**	**.009**	**0.05 – 0.33**					
CBCL Externalizing	0.12 (0.07)	150.63	1.72	.088	−0.02 – 0.26					
CBCL Externalizing × Time	**−0.12 (0.05)**	**86.03**	**−2.43**	**.017**	**−0.21 – −0.02**					

Note. YGTSS = Yale Global Tic Severity Scale; PTQ = Parent Tic Questionnaire; PUTS = Premonitory Urge for Tics Scale; CBCL = Achenbach Child Behavior Checklist 6/18.

Table 5

Linear mixed model repeated measures analysis to identify baseline predictors of change in YGTSS Impairment from baseline through 11-year follow-up: Reduced Model

YGTSS Impairment										
	Estimates of Fixed Effects					**Estimates of Covariance Parameters**				
	Estimate (SE)	**df**	***t***	***p***	**95% CI**		**Estimate (SE)**	**Wald Z**	***p***	**95% CI**
Intercept	27.42 (3.64)	97.53	7.54	<.001	20.21 – 34.64	Repeated Measures AR1 diagonal	49.34 (6.71)	7.35	<.001	37.80 – 64.41
Time	−4.36 (1.29)	77.42	−3.39	.001	−6.92 – −1.80	AR1 rho	−0.13 (0.15)	−0.85	.393	−0.41 – 0.17
Treatment Assignment	−0.40 (1.78)	75.86	−0.23	.820	−3.94 – 3.13	Intercept Variance	26.17 (7.87)	3.33	<.001	14.52 – 47.18
TX Responder Status	−2.90 (1.83)	75.90	−1.58	.118	−6.54 – 0.75					
Evidence-Based Tic TX	−3.06 (1.58)	76.28	−1.94	.056	−6.20 – 0.08					
Sex	−1.31 (2.34)	144.63	−0.56	.576	−5.94 – 3.32					
Sex × Time	**−3.07 (1.42)**	**77.42**	**−2.16**	**.034**	**−5.90 – −0.23**					
Stimulant	−1.84 (2.91)	145.41	−0.63	.529	−7.60 – 3.92					
Stimulant × Time	−2.44 (1.79)	77.42	−1.37	.176	−5.99 – 1.12					
PTQ Total	0.05 (0.05)	143.39	1.08	.281	−0.04 – 0.15					
PTQ Total × Time	0.05 (0.03)	77.42	1.55	.125	−0.01 – 0.11					
PUTS Total	−0.09 (0.15)	144.66	−0.63	.531	−0.38 – 0.20					
PUTS Total × Time	0.16 (0.09)	77.42	1.86	.066	−0.01 – 0.33					
CBCL Externalizing	0.17 (0.10)	144.59	1.73	.087	−0.02 – 0.36					
CBCL Externalizing × Time	**−0.14 (0.06)**	**77.42**	**−2.46**	**.016**	**−0.26 – −0.03**					
BFAM-III Total	0.17 (0.21)	145.71	0.85	.399	−0.23 – 0.58					
BFAM-III Total × Time	0.23 (0.13)	77.42	1.80	.076	−0.02 – 0.48					

Note. YGTSS = Yale Global Tic Severity Scale; PTQ = Parent Tic Questionnaire; PUTS = Premonitory Urge for Tics Scale; CBCL = Achenbach Child Behavior Checklist 6/18; B-FAM-III = Brief-Family Assessment Measure-III.