



RESEARCH ARTICLE

Clinical Utility of Screening for Anxiety and Depression in Children with Tourette Syndrome

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Abstract

Background: Tourette syndrome (TS) is often co-morbid with attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Studies of TS, anxiety and depression have found variable results depending on study methodology and sample characteristics. Our aim was to examine the clinical utility of routine screening for anxiety and depression in children with TS. **Methods:** Using a clinic-based sample, we evaluated the proportion of children with TS meeting diagnostic criteria for ADHD, OCD, generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and major depressive disorder (MDD); the frequency of above average anxiety and depressive symptoms using the Multidimensional Anxiety Scale for Children (MASC) and the Children's Depression Inventory (CDI); and the association between diagnoses and symptom severity. **Results:** One hundred twenty six children were included (mean age 10.7 years). The most common comorbid disorder was ADHD (37%), followed by GAD (21%), OCD (10%), MDD (2%) and SAD (2%). On the MASC, the separation anxiety/panic subscale score was higher than all other subscale scores ($p < 0.0001$). Clinically significant anxiety symptoms were present in 20% of the sample based on the MASC Anxiety Disorders Index, while 6% were identified as potentially clinically depressed based on the CDI Total Score. Yale Global Tic Severity Scale scores were positively correlated with total scores on the MASC ($r = 0.22$, $p = 0.03$) and CDI ($r = 0.37$, $p = 0.0002$). **Conclusions:** Routine screening children with TS for anxiety is warranted given the rate of comorbidity. Screening for depression in TS will have a higher yield in adolescents, adults, and children with more severe tics.

Key Words: *generalized anxiety disorder, major depressive disorder, Tourette Syndrome, tics*

Résumé

Contexte: Le syndrome de Tourette (ST) est souvent comorbide avec le trouble de déficit de l'attention avec hyperactivité (TDAH) et le trouble obsessionnel-compulsif (TOC). Des études du ST, de l'anxiété et de la dépression ont trouvé des résultats variables selon la méthodologie de l'étude et les caractéristiques de l'échantillon. Nous visons à examiner l'utilité clinique du dépistage systématique de l'anxiété et de la dépression chez les enfants souffrant du ST. **Méthodes:** À l'aide d'un échantillon clinique, nous avons évalué la proportion d'enfants souffrant du ST qui satisfaisait aux critères du TDAH, du TOC, du trouble d'anxiété généralisée (TAG), du trouble d'anxiété de séparation (TAS), et du trouble dépressif majeur (TDM); la fréquence de l'anxiété au-dessus de la moyenne et des symptômes dépressifs à l'aide de la Multidimensional Anxiety Scale for Children (MASC) et du Children's Depression Inventory (CDI); et l'association entre les diagnostics et la gravité des symptômes. **Résultats:** Cent vingt-six enfants étaient inclus (âge moyen 10,7 ans). Le trouble comorbide le plus commun était le TDAH (37%), suivi du TAG (21%), du TOC (10%), du TDM (2%) et du TAS (2%). Sur l'échelle MASC, le score à la sous-échelle d'anxiété de séparation/panique était plus élevé que tous les autres scores aux sous-échelles ($p < 0,0001$). Les symptômes d'anxiété cliniquement significatifs étaient présents chez 20% de l'échantillon d'après l'index de troubles anxieux de la MASC, tandis que 6% étaient identifiés comme étant potentiellement cliniquement déprimés d'après

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le score total au CDI. Les scores à la Yale Global Tic Severity Scale étaient positivement corrélés aux scores totaux de la MASC ($r = 0,22$, $p = 0,03$) et du CDI ($r = 0,37$, $p = 0,0002$). **Conclusions:** Le dépistage systématique de l'anxiété chez les enfants souffrant du ST est justifié étant donné le taux de comorbidité. Le dépistage de la dépression dans le ST aura plus de résultats chez les adolescents, les adultes, et les enfants dont les tics sont plus graves.

Mots clés: trouble d'anxiété généralisée, trouble dépressif majeur, syndrome de Tourette, tics

Introduction

Tourette syndrome is a neurodevelopmental disorder characterized by the presence of multiple motor and at least one vocal tic, persisting for at least one year. Once considered a rare disorder, epidemiological studies have shown that approximately seven per 1000 school age children have Tourette syndrome, with boys more commonly affected than girls (Knight et al., 2012). While the basic pathophysiological mechanisms and precise genetic underpinnings responsible for the generation of tics remain obscure, Tourette syndrome is believed to be a heritable disorder related to aberrant activity within the basal ganglia and cortico-striato-thalamocortical loops (Ganos, Roessner, & Munchau, 2013).

Tourette syndrome is uncommonly seen in isolation. The majority of individuals with tics have co-morbid conditions (Freeman et al., 2000), of which attention deficit hyperactivity disorder (ADHD) and obsessive compulsive behaviours or disorder (OCD) are most commonly studied and described, leading to routine screening for these conditions at referral centres. In recent years, there has been increasing research on co-morbid anxiety disorders and depression in individuals with Tourette syndrome. The reported prevalence of comorbid anxiety and depression in individuals with Tourette syndrome has varied considerably between studies, depending on the population studied and study methodology. Population based studies of depression in children and youth suggest that individuals with tics do not have higher rates of depression (Kurlan et al., 2002; Robertson, 2006), while clinically ascertained samples demonstrate depressive symptoms which are often correlated with tic severity, comorbid OCD diagnoses, and older age (Chou, Lin, Lin, Sung, & Kao, 2013; Mol Debes, Hjalgrim, & Skov, 2008; Robertson, Williamson, & Eapen, 2006). In contrast, both population-based (Kurlan et al., 2002) and clinically ascertained samples (Coffey et al., 2000) show higher rates of anxiety disorders in children and youth with Tourette syndrome, as well as correlations between tic severity and anxiety symptoms or diagnoses (Coffey et al., 2000; Johnco et al., 2016). Some studies have focused on self-reported symptoms of anxiety or depression without confirmation of clinical diagnoses of these conditions (Mol Debes et al., 2008; Robertson et al., 2006). A recent study of 1374 children and adults with TS participating in genetic studies found that the lifetime prevalence

of anxiety disorders was 36.1%, and mood disorders was 29.8% (Hirschtritt et al., 2015).

In the present study, we aimed to determine the utility of routine screening for anxiety and depression in children and youth with Tourette Syndrome by: (1) evaluating the proportion of referred children and adolescents with tics that meet diagnostic criteria for a comorbid anxiety or depression diagnosis; (2) examining the frequency of above average anxiety and depressive symptoms in children with tics; (3) exploring the association between an anxiety disorder diagnosis and comorbid ADHD and OCD diagnoses, age, and gender; and, (4) assessing the relationship between tic severity and the severity of anxiety and depressive symptoms. Based on clinical experience at our referral centre, we hypothesized that more children with chronic tic disorders would have a comorbid anxiety disorder diagnosis than comorbid depression; that more children would have above average anxiety symptoms than depressive symptoms; and that children with greater tic severity and related impairment would have more severe anxiety and depressive symptoms.

Materials and Methods

Approval for the study was obtained from the University of Calgary Conjoint Health Regional Ethics Board. This study included 126 children and adolescents meeting DSM-IV-TR criteria for Tourette's disorder, chronic motor tic disorder, or chronic vocal tic disorder who were consecutively evaluated at a Tourette syndrome clinic over a two year period. All children were evaluated using a structured clinical interview based on DSM-IV-TR criteria by a neurologist subspecializing in movement disorders and neuropsychiatry. Pre-existing psychiatric diagnoses of ADHD, OCD, major depressive disorder, generalized anxiety disorder, and separation anxiety disorder were confirmed during the interview, and all new diagnoses of these disorders were made as part of clinical assessment procedures for treatment planning. We evaluated the proportion of children who met DSM-IV-TR criteria for the following comorbid conditions: ADHD, OCD, generalized anxiety disorder, separation anxiety disorder, and major depressive disorder.

All children completed the Multidimensional Anxiety Scale for Children (MASC), the Children's Depression Inventory (CDI), and the Children's Yale-Brown Obsessions and Compulsion Checklist. Parents and teachers completed the

Conners 3 Short for ADHD symptoms. A clinical nurse specialist in Tourette syndrome completed the Yale Global Tic Severity Scale (YGTSS).

The MASC is a self-report instrument that screens for major anxiety symptoms in children (March, 1997). It consists of 39 items distributed across four basic scales, the total anxiety scale, and the anxiety disorders index. The physical symptom scale consists of two subscales, the tense symptoms scale which reports symptoms such as feeling uptight, and the somatic symptoms scale which reports symptoms such as dizziness or heart racing. The harm avoidance scale consists of the perfectionism scale that measures symptoms such as trying extra hard to do everything right, and the anxious coping scale that measures symptoms such as checking to make sure things are safe. The social anxiety scale consists of the humiliation fears scale that assesses worries such as other people laughing at the respondent, and the performance fears scale which assesses worries such as getting called on in class. The separation/panic scale evaluates preference to stay close to family members or at home, fears of being alone or in unfamiliar situations, and somatic/autonomic symptoms. The total anxiety score reports on the symptoms across all anxiety scales. The anxiety disorders index consists of a set of items that are found to differentiate children with a diagnosis of an anxiety disorder from children without a diagnosis. The MASC generates raw scores that are converted to standard *T*-scores with a mean of 50 and a standard deviation of ten in all samples and across all scales. Scores are compared to age and sex based norms. *T*-scores above 65 are much above average and are likely to represent clinically significant symptoms.

We calculated the mean *T*-score for each subscale of the MASC, the proportion of children with *T*-scores over 65 (signifying much above average symptoms) on each scale, and the proportion of children with *T*-scores over 65 for the anxiety disorders index. Mean *T*-scores on the anxiety disorders index were compared between children (age less than 13 years) and adolescents using a *t*-test. We performed a multivariate test of means to assess for differences in the mean score between the four basic scale scores to determine if there were specific types of anxiety symptoms that were more prominent in children with Tourette syndrome. The association between the diagnosis of a comorbid anxiety disorder and the diagnosis of ADHD, OCD, sex, and age (less than 13 versus age 13 and older) was assessed by calculating odds ratios and the chi-squared test. We examined the linear relationship between the tic severity and related impairment (YGTSS score) and the severity of anxiety symptoms (MASC total score) using the Pearson correlation.

The CDI is a self report instrument (Kovacs, 2001) consisting of 27 items distributed across five scales, as well as a total score. CDI *T*-scores are based on a normative sample of 1266 youth and are calculated based on age and sex. CDI

T-scores of 65 to 69 are considered elevated and above 70 are considered very elevated and identify potentially clinically depressed individuals. The negative mood subscale reflects feeling sad, worrying, and being unable to make up one's mind. The interpersonal problems subscale reflects problems and difficulties with people, social avoidance, and isolation. The ineffectiveness subscale reflects a negative evaluation of one's ability and school performance. The anhedonia subscale reflects impaired ability to experience pleasure, loss of energy, and problems with sleeping and appetite. The negative self-esteem subscale reflects low self-esteem, self-dislike, and feelings of being unloved. We calculated the mean score on each subscale of the CDI, and the proportion of children with scores over 65 on each individual subscale as well as the CDI total score. Mean *T*-scores on the CDI total were compared between children (age less than 13 years) and adolescents using a *t*-test. We examined the linear relationship between tic severity and related impairment (YGTSS score) and the severity of depressive symptoms (CDI total score) using the Pearson correlation. Finally, we calculated the prevalence risk ratio for being diagnosed with generalized anxiety disorder versus depression in our sample.

Results

One hundred and twenty six children were included in the study. The mean age of participants was 10.7 years (SD 3.0), with an age range from five to 17 years. Boys accounted for 99 of the 126 participants (78.6%). All children met diagnostic criteria for Tourette syndrome, chronic motor tic disorder or chronic vocal tic disorder. The mean YGTSS score was 32.1 out of 100 points (95% CI 28.1-36.2). There was no significant difference in YGTSS scores between children and adolescents.

Comorbid diagnoses are presented in Table 1. The most common comorbid condition diagnosed was ADHD, which was present in 37%, followed by generalized anxiety disorder, obsessive compulsive disorder, depression and separation anxiety disorder.

On the MASC, the separation/panic subscale had the highest mean score at 58.4 (95%CI 56.0-60.9) (see Table 2). Multivariate test of means revealed that the separation/panic subscale score was significantly higher than all other subscale scores (Probability > $F = 0.0001$). Separation/panic subscale scores were over 65 in 31.8% of the sample, signifying much above average symptoms in this domain. Nearly 20% of the sample scored over 65 on the anxiety disorders index. Children had significantly lower scores on the anxiety disorders index than adolescents ($p=0.03$). Children and adolescents with generalized anxiety were more likely to have a score over 65 on the anxiety disorders index, with an odds ratio of 6.29 (95% CI 2.09-18.61, $Pr > \chi^2 = 0.0001$).

Tests for associations between a comorbid generalized anxiety disorder diagnosis and comorbid ADHD, comorbid

Table 1. Frequency of comorbid psychiatric diagnoses		
	Number of children	Percentage of total
ADHD	47/126	37.3%
Generalized anxiety Disorder	26/126	20.6%
Obsessive compulsive disorder	12/126	9.5%
Depression	3/126	2.4%
Separation anxiety disorder	2/126	1.6%

Table 2. Multidimensional Anxiety Scale for Children Subscale scores		
Subscale	Mean Subscale Score	Proportion of Subjects Subscale Score over 65
Tense symptoms	52.6 95% CI 50.7-54.5	14.3%
Somatic symptoms	48.2 95% CI 46.4-50.0	8.7%
Physical symptoms	50.5 95% CI 48.6-52.3	10.3%
Perfectionism	51.5 95% CI 49.8-53.2	3.2%
Anxious coping	53.0 95% CI 51.1-54.9	12.7%
Harm avoidance	52.7 95% CI 50.9-54.5	11.9%
Humiliation fears	54.6 95% CI 52.5-56.8	26.2%
Performance fears	51.5 95% CI 49.6-53.3	9.5%
Social anxiety	53.7 95% CI 51.8-55.7	16.7%
Separation/panic	58.4 95%CI 56.0-60.9*	31.8%
MASC total	54.7 95%CI 52.7-56.7	18.3%
Anxiety disorders index	54.5 95% CI 52.5-56.6	19.1%

*Significantly higher than all other subscale scores, p=0.0001

Table 3. Children's Depression Inventory Subscale scores		
Subscale	Mean Subscale Score	Proportion of Subjects Subscale Score over 65
Negative mood	48.3 95% CI 46.5-50.1	9.5%
Interpersonal problems	48.8 95% CI 47.4-50.2	2.4%
Ineffectiveness	48.2 95% CI 46.8-49.6	1.6%
Anhedonia	49.4 95% CI 47.7-51.2	10.3%
Negative self-esteem	46.1 95% CI 44.7-47.5	6.4%
Total score	47.7 95% CI 46.0-49.4	6.4%

OCD, sex and age (less than 13, age 13 and older) revealed a significant association with comorbid OCD only, with an odds ratio 10.7 (95% CI 2.5-52.2, $Pr > \chi^2 < 0.0001$). Children with OCD were ten times more likely to be diagnosed with generalized anxiety disorder than children without OCD. There was a significant positive linear relationship between the MASC total T score and the YGTSS score, with a Pearson correlation of 0.22 ($p=0.03$).

On the CDI, overall, fewer children had elevated (T score 65 or higher) subscale or total scores (see Table 3). Only 6.4% of the sample had a T score over 65 on the CDI Total, the recommended cut-off for identifying potentially clinically

depressed individuals. Children with depression were more likely to have a T score over 65 on the CDI Total, with an odds ratio of 39.0 (95% CI 1.6-2317.6, $Pr > \chi^2 < 0.0001$). There was no significant difference in mean T scores on the CDI Total between children and adolescents. There was a significant positive correlation between the CDI total T score and the YGTSS score, with a Pearson correlation of 0.37 ($p=0.0002$).

Children with tics were nearly nine times more likely to meet diagnostic criteria for generalized anxiety disorder than depression, risk ratio 8.7 (95%CI 2.7-27.9, $Pr > \chi^2 < 0.0001$).

Discussion

Our study of a clinic based sample of children with Tourette syndrome and chronic tic disorders demonstrated that symptoms and diagnoses of generalized anxiety disorder are more common than symptoms and diagnoses of depression. Generalized anxiety disorder was the second most common comorbid condition in our sample, with more children meeting diagnostic criteria for generalized anxiety disorder than OCD.

Our results are consistent with a community-based study assessing comorbid psychopathology in children with tics (Kurlan et al., 2002). In this school-based study in New York state, overanxious disorder (diagnosis now subsumed under generalized anxiety disorder) was present in 21.2% of children with tics, which was more common than OCD (10.9%) and major depressive disorder (9.7%). The authors of this study state that the low rate of OCD observed in their study may have been due to fact that their sample was restricted to children, and symptoms meeting OCD diagnostic criteria may not have developed yet. Longitudinal studies have shown that OCD symptoms tend to peak later than tic symptoms (Bloch et al., 2006), and that the prevalence of OCD in the general population is significantly higher in 13 to 15 year olds compared to younger children (Ford, Goodman, & Meltzer, 2003). As the mean age of our study participants was even younger at 10.7 years, the comorbidity rate of OCD of 9.5% is not unexpected. Our study found that children with OCD had a significantly higher odds of having generalized anxiety disorder. This is consistent with population-based prevalence studies of OCD, where comorbid generalized anxiety disorder has been diagnosed in more than 50% of children meeting diagnostic criteria for OCD (Canals, Hernandez-Martinez, Cosi, & Voltas, 2012; Heyman et al., 2001).

Population-based prevalence studies of mental health disorders in children and adolescents consistently demonstrate that while non-OCD anxiety disorders tend to peak between the age of eight to 12, depressive disorders peak later in adolescence (from age 15) and continue increasing into adulthood (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Ford et al., 2003). Studies of adults with Tourette have been able to demonstrate a more consistent association between Tourette syndrome, depression diagnoses, and related functional impairment (Jalenques et al., 2012; Lewin et al., 2011; Piedad, 2016). In contrast, studies in children and youth have reported inconsistent associations between Tourette syndrome and depression, likely due to differences between studies in the mean age of the included sample, symptom severity of the included sample, and the screening instruments used. A study of comorbid disorders in youth with Tourette syndrome using the Tourette Syndrome International Database Consortium found that the prevalence of mood disorders increased in each successive age group studied, with the highest rates reported in 14 to 17 year olds

(Wanderer et al., 2012). A population based cohort study in Taiwan evaluating comorbid depression in youth with Tourette syndrome found that the mean age at depression diagnosis was 14.4 years (Chou et al., 2013). A clinic based study of 314 children in Denmark reported that 26.5% of children were suspected to have depression based on scores higher than the normative 95th percentile on ten items on the Child Behaviour Checklist (Mol Debes et al., 2008). These ten items however assess symptoms of anxiety as well as depression, and diagnoses of depression were not confirmed clinically. A more recent study of 98 children with Tourette Syndrome reported that 15.3% scored above 16 on the CDI, all of whom were older than 13 years (Rizzo, Gulisao, Martino, & Robertson, 2017). A cut-off score of 16 on the CDI has been suggested by some investigators to have optimal sensitivity and specificity for the screening of depression in children and adolescents, while others have suggested a higher cut-off score of 19 (Timbremont, Braet, & Dreessen, 2004). In our study, three of 126 children had confirmed clinical diagnoses of depression. Using the CDI developer's recommended age and sex normed T-score of 65 as the indicator of potentially clinically depressed individuals, eight of 126 children screened positive for depression, with six false positives, and one false negative. Using a cut-off of 16 on the CDI total score, 21 of 126 of our subjects would have screened positive for depression, with 18 false positives and no false negatives. These results highlight the utility of the CDI as a screening measure, in which sensitivity is of prime importance. The CDI however should not be used to make a diagnosis of depression, as many children and youth with elevated scores on the CDI will not ultimately meet diagnostic criteria.

We found a significant correlation between tic severity as measured with the YGTSS and the severity of depressive symptoms on the CDI. The correlation observed with tic severity was stronger for depressive than anxiety symptom severity. Using the same two measures of symptom severity, the YGTSS and the CDI, Cohen et al observed a similar correlation of 0.41 ($p < 0.01$) in 45 children with Tourette syndrome (Cohen, Sade, Benarroch, Pollak, & Gross-Tsur, 2008). In contrast, no correlation between tic severity and the severity of anxiety symptoms was observed. Robertson et al also reported a significant correlation between YGTSS and CDI scores (Robertson et al., 2006). Together these results suggest that screening for depression in children and youth with TS with more severe tics is likely to have greater yield.

Our study suggests that in the prepubertal child with Tourette syndrome or chronic tics, the major comorbid diagnoses to be addressed are ADHD and generalized anxiety disorder. A qualitative study with youth with Tourette syndrome found that young people feel anxious and worried about their tics (which worsens the tics) and that the anxiety-related emotions associated with tics are distressing (Cuenca et al., 2015). Both our study and previous

studies (Coffey et al., 2000; Johnco et al., 2016; Kurlan et al., 2002) suggest that tic severity is worse in individuals with co-morbid anxiety symptoms. Disentangling the cause effect relationship between tics and anxiety is challenging and ideally, treatments aimed at targeting both tic and anxiety symptoms may result in more favourable responses. The success of the Comprehensive Behavioural Intervention for Tics, which includes not only habit reversal training but also relaxation training and a functional intervention to address situations that sustain or worsen tics, suggests this may be true (Piacentini et al., 2010). Furthermore, other behavioural interventions used in the treatment of anxiety disorders have encouraging pilot data in individuals with tics, including mindfulness based stress reduction (Reese et al., 2015) and acceptance and commitment therapy (Franklin, Best, Wilson, Loew, & Compton, 2011).

The children in our sample scored significantly higher on the separation/panic subscale of the MASC than on all the other subscales. The separation/panic scale evaluates preference to stay close to family members or at home, fears of being alone or in unfamiliar situations, and somatic/autonomic symptoms. Other studies have reported a high prevalence of separation anxiety, including a community-based study in which separation anxiety symptoms were present in 14.8% of the children with tics and only 7.2% of children without tics (Kurlan et al., 2002). Another clinic-based study in children with Tourette syndrome reported a higher prevalence of both panic disorder and separation anxiety in children with severe tics than in children with mild to moderate tics. They also found that separation anxiety disorder was the disorder that most robustly predicted tic severity (Coffey et al., 2000). The association between separation anxiety symptoms and tic disorders may be the result of embarrassment due to tics in social situations, and efforts to suppress tics, resulting in feelings of stress or mental fatigue.

First-line treatment for anxiety disorders in children and adolescents is Cognitive Behavioral Therapy (CBT). For severe cases of anxiety, a combination of CBT and medical treatment with sertraline is suggested (Connolly et al., 2007). A randomized placebo-controlled study in children with separation or generalized anxiety disorder found much improvement in 60% of the patients who had received CBT and in 55% of the sertraline group, compared to 24% in the placebo group. In children receiving combination-therapy (both CBT and sertraline), improvement in 81% was reported (Walkup et al., 2008). The potential for SSRIs to exacerbate tics should be considered when treating generalized anxiety disorder in children with Tourette syndrome (Hauser & Zesiewicz, 1995; Kurlan, Como, Deeley, McDermott, & McDermott, 1993; Rua & Damasio, 2014). CBT should be the favoured treatment of anxiety disorders in children and adolescents with Tourette syndrome due to its proven efficacy without risk of tic worsening.

Limitations of the current study include its clinic-based sample. Our findings may not apply to children and adolescents in the community with chronic tic disorders. While our clinic is a regional referral centre, children with the full spectrum of disease severity are evaluated and the mean tic severity scale of our sample was in the mild to moderate range. Furthermore, the rates of comorbidity seen in our sample are similar to community-based studies of children with tics. Our study is also limited by its cross-sectional nature, and does not include any longitudinal outcome data regarding tics or other psychiatric symptom outcomes.

Conclusion

In conclusion, our study and the previous literature suggest that routine screening of children with chronic tic disorders for anxiety is warranted given the high rate of comorbidity and the relationship between anxiety and tic severity. Given the strong reciprocal relationship between tic and anxiety symptoms, strategies that attempt to address both types of symptoms may result in better treatment responses. The results of our study suggest elevated depressive symptoms and depression diagnoses are less common than anxiety in children with tics. Screening for depression in individuals with chronic tic disorders is likely to have a higher yield in adolescents, adults, and individuals with severe tics.

Acknowledgements / Conflicts of Interest

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References

- Bloch, M. H., Peterson, B. S., Scahill, L., Otko, J., Katsovich, L., Zhang, H., & Leckman, J. F. (2006). Adult outcome of tic and obsessive-compulsive symptom severity in children with Tourette Syndrome. *Archives of Pediatric and Adolescent Medicine*, 2006(160), 65-69.
- Canals, J., Hernandez-Martinez, C., Cosi, S., & Voltas, N. (2012). The epidemiology of obsessive-compulsive disorder in Spanish school children. *Journal of Anxiety Disorders*, 26, 746-752.
- Chou, I., Lin, H., Lin, C., Sung, F., & Kao, C. (2013). Tourette Syndrome and Risk of Depression: A Population-Based Cohort Study in Taiwan. *Journal of Developmental & Behavioral Pediatrics*, 34(181-185).
- Coffey, B. J., Biederman, M. D., Smoller, J. W., Geller, D. A., Sarin, P., Schwartz, S., & Kim, G. S. (2000). Anxiety Disorders and Tic Severity in Juveniles With Tourette's Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(5), 562-568.
- Cohen, E., Sade, M., Benarroch, F., Pollak, Y., & Gross-Tsur, V. (2008). Locus of control, perceived parenting style, and symptoms of anxiety and depression in children with Tourette's syndrome. *European Child and Adolescent Psychiatry*, 17, 299-305.
- Connolly, S. D., Bernstein, G. A., Bernet, W., Buckstein, O., Arnold, V., Beitchman, J.,...Ptakowski, K. K. (2007). Practice Parameter for Assessment and Treatment of Children and Adolescents With Anxiety Disorders. *Journal of American Academy of Child and Adolescent Psychiatry*, 46(2), 267-283.

- Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. *Archives of General Psychiatry*, *60*, 837-844.
- Cuenca, J., Glazebrook, C., Kendall, T., Hedderly, T., Heyman, I., Jackson, G.,...Hollis, C. (2015). Perceptions of treatment for tics among young people with Tourette syndrome and their parents: A mixed methods study. *BMC Psychiatry*, *15*, 46. doi:10.1186/s12888-015-0430-0
- Ford, T., Goodman, R., & Meltzer, H. (2003). The British Child and Adolescent Mental Health Survey 1999: The Prevalence of DSM-IV Disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *42*(10), 1203-1211.
- Franklin, M. E., Best, S. H., Wilson, M. A., Loew, B., & Compton, S. N. (2011). Habit Reversal Training and Acceptance and Commitment Therapy for Tourette Syndrome: A Pilot Project. *Journal of Developmental and Physical Disabilities*, *23*(1), 49-60. doi:10.1007/s10882-010-9221-1
- Freeman, R. D., Fast, D. K., Burd, L., Kerbeshian, J., Robertson, M. M., & Sandor, P. (2000). An international perspective on Tourette syndrome: Selected findings from 3500 individuals in 22 countries. *Developmental Medicine & Child Neurology*, *42*, 436-447.
- Ganos, C., Roessner, V., & Munchau, A. (2013). The functional anatomy of Gilles de la Tourette syndrome. *Neuroscience and Biobehavioral Reviews*, *37*(6), 1050-1062. doi:10.1016/j.neubiorev.2012.11.004
- Hauser, R., & Zesiewicz, T. A. (1995). Sertraline-Induced Exacerbation of Tics in Tourette's Syndrome. *Movement Disorders*, *10*(5), 682-684.
- Heyman, I., Fombonne, E., Simmons, H., Ford, T., Meltzer, H., & Goodman, R. (2001). *British Journal of Psychiatry*, *179*, 324-329.
- Hirschtritt, M. E., Lee, P. C., Pauls, D. L., Dion, Y., Grados, M. A., Illmann, C.,...Tourette Syndrome Association International Consortium for, G. (2015). Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry*, *72*(4), 325-333. doi:10.1001/jamapsychiatry.2014.2650
- Jalenques, I., Galland, F., Malet, L., Morand, D., Legrand, G., Auclair, C.,...Durif, F. (2012). Quality of life in adults with Gilles de la Tourette Syndrome. *BMC Psychiatry*, *12*(109).
- Johnco, C., McGuire, J. F., McBride, N. M., Murphy, T. K., Lewin, A. B., & Storch, E. A. (2016). Suicidal ideation in youth with tic disorders. *Journal of Affective Disorders*, *200*, 204-211.
- Knight, T., Steeves, T., Day, L., Lowerison, M., Jette, N., & Pringsheim, T. (2012). Prevalence of tic disorders: A systematic review and meta-analysis. *Pediatric Neurology*, *47*, 77-90.
- Kovacs, M. (2001). *Children's Depression Inventory: Technical Manual*. Toronto, Canada: Multi-Health Systems Inc.
- Kurlan, R., Como, P. G., Deeley, C., McDermott, M., & McDermott, M. P. (1993). A Pilot Controlled Study of Fluoxetine for Obsessive-Compulsive Symptoms in Children with Tourette's Syndrome. *Clinical Neuropharmacology*, *16*(2), 167-172.
- Kurlan, R., Como, P. G., Miller, B., Palumbo, D., Deeley, C., Andresen, E. M.,...McDermott, M. P. (2002). The behavioral spectrum of tic disorders. A community-based study. *Neurology*, *59*, 414-420.
- Lewin, A. B., Storch, E. A., Conelea, C. A., Woods, D. W., Zinner, S. H., Budman, C. L.,...Murphy, T. K. (2011). The roles of anxiety and depression in connecting tic severity and functional impairment. *Journal of Anxiety Disorders*, *25*, 164-168.
- March, J. S. (1997). *Multidimensional anxiety scale for children. Technical manual*. Toronto, Canada: Multi-Health Systems Inc.
- Mol Debes, N. M. M., Hjalgrim, H., & Skov, L. (2008). Validation of the Presence of Comorbidities in a Danish Clinical Cohort of Children with Tourette Syndrome. *Journal of Child Neurology*, *23*(9), 1017-1027.
- Piacentini, J., Woods, D. W., Scahill, L., Wilhelm, S., Peterson, A. L., Chang, S.,...Walkup, J. T. (2010). Behaviour therapy for children with Tourette Disorder: A Randomized Controlled Trial. *JAMA*, *303*(19), 1929-1937.
- Piedad, J. C. P. C., A.E. (2016). Depression in Tourette syndrome: A controlled and comparison study. *Journal of Neurological Sciences*, *364*, 128-132.
- Reese, H. E., 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*(3), 293-298. doi:10.1016/j.jpsychores.2014.08.001
- Rizzo, R., Gulisao, M., Martino, D., & Robertson, M. (2017). Gilles de la Tourette Syndrome, Depression, Depressive Illness, and Correlates in a child and adolescent population. *Journal of Child and Adolescent Psychopharmacology*, epub ahead of print.
- Robertson, M. (2006). Mood disorders and Gilles de la Tourette's syndrome: An update on prevalence, etiology, comorbidity, clinical associations, and implications. *Journal of Psychosomatic Research*, *61*, 349-358.
- Robertson, M., Williamson, F., & Eapen, V. (2006). Depressive symptomatology in young people with Gilles de la Tourette Syndrome: A comparison of self-report scales. *Journal of Affective Disorders*, *91*, 265-268.
- Rua, A., & Damasio, J. (2014). Tics Induced by Sertraline: Case Report and Literature Review. *International Parkinson and Movement Disorder Society*.
- Timbremont, B., Braet, C., & Dreessen, L. (2004). Assessing depression in youth: Relation between the children's depression inventory and a structured interview. *Journal of Clinical Child and Adolescent Psychology*, *33*(1), 149-157.
- Walkup, J., Albano, A. M., Piacentini, J., Birmaher, B., Compton, S. N., Sherrill, J. T.,...Kendall, P. C. (2008). Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety. *The New England Journal of Medicine*, *359*(26), 2753-2766.
- Wanderer, S., Roessner, V., Freeman, R., Bock, N., Rothenberger, A., & Becker, A. (2012). Relationship of Obsessive-Compulsive Disorder to Age-Related Comorbidity in Children and Adolescents With Tourette Syndrome. *Journal of Developmental & Behavioral Pediatrics*, *33*, 124-133.