Comorbidity in people with Tourette syndrome

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Objectives

1. To discuss the most common comorbid conditions in people with TS

2. To review how comorbid ADHD and OCD affect treatment decisions

Comorbidity in TS

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Lifetime Prevalence, Age of Risk, and Etiology of Comorbid Psychiatric Disorders in Tourette Syndrome

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Hirschtritt et al. 2015

Largest and most comprehensive study of comorbidity in people with TS

Cross-sectional structured diagnostic interviews conducted in participants with TS (n = 1374) and TS-unaffected family members (n = 1142) from tic disorder specialty clinics in the United States, Canada, Great Britain, and the Netherlands

Main Outcomes and Measures

Lifetime prevalence of comorbid DSM-IV-TR disorders, their heritabilities, ages of maximal risk, and associations with symptom severity, age at onset, and parental psychiatric history

Overall burden of psychiatric comorbidity

85.7% met the criteria for 1 or more comorbid disorder

57.7% met the criteria for 2 or more comorbid disorders

OCD and ADHD

The most common comorbid psychiatric disorders were OCD (50.0%) and ADHD (54.3%)

Females were more likely to have comorbid OCD (57.1% vs 47.5%; $P < .01$)

Males were more likely to have comorbid ADHD (58.5% vs 42.3%; $P < .01$)

29.5% of the participants had TS+OCD+ADHD

TS/CMVTD, OCD, and ADHD all demonstrated significant genetic correlations

Other conditions

After OCD and ADHD, mood disorders, anxiety disorders, and disruptive behaviour disorders were the most prevalent classes of psychiatric comorbidity, each affecting approximately 30%

Psychotic disorders were the least common (<1%)

Females were more likely to have major depressive disorder, most anxiety disorders, and eating disorders

Males were more likely to have ADHD, oppositional defiant disorder or conduct disorder

Adults and adolescents were more likely to have OCD as well as mood, anxiety, eating, and substance use disorders

Children were more likely to have ADHD

ADHD

DSM V Criteria for ADHD

People with ADHD show a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development

Inattention: Six or more symptoms of inattention < 16, or five or more for 17+

Symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level

Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity < 16 years, or five or more for 17+

Symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level

Inattention

Often fails to give close attention to details or makes careless mistakes	Often has trouble holding attention on tasks or play activities.	Often does not seem to listen when spoken to directly.
Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	Often has trouble organizing tasks and activities.	Often avoids, dislikes, or is reluctant to do tasks that require mental effort over long periods
Often loses things necessary for tasks and activities	Is often easily distracted	Is often forgetful in daily activities.

Hyperactivity/Impulsivity

- Often fidgets with or taps hands or feet, or squirms in seat.
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often leaves seat in situations when remaining seated is expected.
- Is often "on the go" acting as if "driven by a motor".
- Often has trouble waiting their turn.
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
- Often unable to play or take part in leisure activities quietly.
- Often interrupts or intrudes on others (e.g., butts into conversations or games)

DSM V Criteria for ADHD

- Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
- Several symptoms are present in two or more settings, (such as at home, school or work).
- There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
- The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).
- The symptoms do not happen only during the course of schizophrenia or another psychotic disorder.

DSM V Criteria for ADHD

Combined Presentation: if enough symptoms of both criteria inattention and hyperactivity-impulsivity were present for the past 6 months

Predominantly Inattentive Presentation: if enough symptoms of inattention, but not hyperactivity-impulsivity, were present for the past six months

Predominantly Hyperactive-Impulsive Presentation: if enough symptoms of hyperactivity-impulsivity, but not inattention, were present for the past six months.

Comorbid ADHD in people with TS

Approximately 50% of people with TS are diagnosed with ADHD

ADHD symptoms and diagnosis usually precede tic onset

Lower rates of comorbidity are seen in community derived samples 25-35%

Comorbidity rates between tics and ADHD are higher with more severe tic disorders

transient tics < chronic motor tic disorder < chronic vocal tic disorder < TS

TS and ADHD: Shared Symptomatology

Impairment in attention

Impairment in control

Hyperactivity

Anxiety

Behaviour problems

Obsessive compulsive behaviours

Sensory processing issues

Depression

Sleep disturbances

Impairment in socialization and communication

Repetitive patterns of behaviour

TS and ADHD: Shared Etiology?

Evidence suggests similar neuropathology between TS and ADHD – long-range underconnectivity and short-range overconnectivity

In normal brain development, a shift occurs from local processing (short-range connectivity) to more global processing (long-range connectivity)

With age there is pruning of local connectivity and strengthening of long-range connectivity

Brain connectivity issues could be due to neuronal insult or genetically determined

Deficits in brain connectivity correlate with both tic and ADHD symptom severity

Contrasting TS+ADHD vs ADHD only

- ADHD severity is minimally greater in children with TS+ ADHD compared to children with ADHD only
- Age of ADHD onset is similar
- Frequency of mood disorders, anxiety disorders and disruptive behaviour disorders is similar in children with TS+ADHD and ADHD only
- Frequency of OCD is higher in children with TS+ADHD than children with ADHD only

How does the co-occurrence of ADHD impact children with TS?

Children with ADHD+TS seem to be treated for TS symptoms earlier, without having greater tic severity. May be related to greater overall psychosocial impairment.

Co-occurring ADHD may impair tic suppression

Mental effort to suppress tics may accentuate inattention in ADHD

Presence of comorbid ADHD may moderate the effectiveness of alpha agonists for the treatment of tics – studies suggest greater effect of alpha agonists for tics in children with TS+ADHD

Risk for aggressive and delinquent behaviour and conduct difficulties in children with TS is posed largely by the presence of ADHD

Greatest independent predictor of psychosocial quality of life in children with TS is ADHD symptom severity

Treatment priority: TS vs ADHD

ADHD symptoms usually cause greater impairment in cognitive, emotional and social skills than tics, unless tics are very severe

Treatment should prioritize the symptoms causing the most impairment

Treating ADHD in children with tics

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[Intervention Review]

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

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Treating ADHD in children with tics

Objective: To assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorders on symptoms of ADHD and tics

Methods: Systematic review of randomized controlled trials of any pharmacological treatment for ADHD used specifically in children with ADHD+TS

Treating ADHD in children with tics

8 randomized controlled trials with 510 participants – 443 boys, 67 girls

All studies performed in USA

Trial length ranged from 3 to 22 weeks

Several trials assessed multiple agents

Medications assessed included methylphenidate, clonidine, desipramine, dextroamphetamine, guanfacine, atomoxetine and deprenyl

Methylphenidate

Outcomes	Effect of treatment	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
ADHD symptom-related behavior Measured by standardized rating scales: Conners' Abbreviated Teacher Rating Scale, Conners' Abbreviated Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Mothers' Objective Method for Subgrouping, Continuous Performance Task, Conners' Teacher Rating Scale, Conners' Continuous Performance Task	Tourette's Syndrome Study Group 2002 showed a significant treatment effect using the Conners' Abbreviated Teacher Rating Scale (3.3 points, 98.3% CI −0.2 to 6.8; P = 0.02). Gadow 2007 showed that all doses (0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg) of methylphenidate were superior to placebo on all rating scales (Conners' Abbreviated Teacher/Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Mothers' Objective Method for Subgrouping, Continuous Performance Test), with a dose-dependent effect (F = 24.7; P = 0.001) Castellanos 1997 showed significantly decreased hyperactivity at all doses (15 mg, 25 mg, 45 mg).	229 (3 studies)	⨁⨁◯◯ **Low**[a]	–

Methylphenidate

Tic severity Measured by standardized rating scales: Yale Global Tic Severity Scale, Tourette Syndrome Severity Scale, Tourette Syndrome Clinical Global Impression Scale, Global Tic Rating Scale, 2-Minute Tic and Habit Count, Tic Symptom Self-Report	Tourette's Syndrome Study Group 2002 found a significant treatment effect using the Yale Global Tic Severity Scale (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003). Gadow 2007 found no difference on the Yale Global Tic Severity Scale but found an improvement in tic severity at all doses (0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg) on the Global Tic Rating Scale completed by teachers (F = 5.33; P = 0.002) Castellanos 1997 found no effect of drug on tic severity for second and third cohorts. Tic severity was significantly greater during week 2 in the first cohort (P < 0.01)	229 (3 studies)	⨁⨁◯◯ **Low**[a]	–

Tourette syndrome study group

RCT in 136 children with TS+ADHD for 16 weeks

Randomized to clonidine alone, methylphenidate alone, combined clonidine and methylphenidate, or placebo

ADHD symptom improvement on ASQ-Teacher

Clonidine alone vs placebo 3.3 (-0.2, 6.8)

Methylphenidate alone vs placebo 3.3 (-0.2, 6.8)

Clonidine + methylphenidate vs placebo 6.3 (2.8, 9.8)

Tourette syndrome study group

- Tic severity on Yale Global Tic Severity Scale
- Clonidine vs placebo 10.9 (2.1, 19.7)
- Methylphenidate vs placebo 9.4 (0.7, 18.1)
- Clonidine + Methylphenidate vs placebo 11.0 (2.1, 19.8)

Tourette syndrome study group

Worsening tics reported as an adverse effect in:

20% of children receiving methylphenidate

22% of children receiving placebo

26% of children receiving clonidine alone

Tourette syndrome study group

Tics limited further dosage increases more often for participants assigned to methylphenidate alone (35%), than participants assigned to methylphenidate plus clonidine (15%), clonidine alone (18%) or placebo (19%)

Tourette syndrome study group

Data from Tourette syndrome study group suggest methylphenidate and clonidine have similar efficacy in treating ADHD symptoms, and that their combination is superior to either treatment alone

These findings are contrary to clinical experience, in which stimulants are more effective than alpha agonists in most patients

Unexpected result may be due to low doses of methylphenidate used in the study of 25 mg/day

Dextroamphetamine

One placebo-controlled crossover study of dextroamphetamine including 20 children

Assessed doses of 7.5 mg BID, 15 mg BID or 22.5 mg BID

Increased tic severity seen with 15 mg BID and 22.5 mg BID dose

Improved ADHD symptom severity seen with all three doses

Clonidine

Outcomes	Effect of treatment	Number of participants (studies)	Quality of the evidence (GRADE)
ADHD symptom-related behavior Measured by standardized rating scales: Conners' Abbreviated Teacher Rating Scale, Conners' Abbreviated Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Conners' Continuous Performance Task, Child Behaviour Checklist, Gordon Diagnostic System, Clinical Evaluation of Language Function, Matching Familial Figures Test, Porteus Maze Test, Restricted Academic Test	Tourette's Syndrome Study Group 2002 found a significant treatment effect using the Conners' Abbreviated Teacher Rating Scale (3.3 points, 98.3% CI −0.2 to 6.8; P = 0.02). Singer 1995 found no significant difference on any ADHD outcome measures, except the nervous/overactive subscale of the Child Behaviour Checklist (boys aged 6-11 years).	170 (2 studies)	⊕⊕⊖⊖ **Low**[a]

Clonidine

Tic severity Measured by standardized rating scales: Yale Global Tic Severity Scale, Tourette Syndrome Severity Scale, Global Tic Rating Scale, Tic Symptom Self-Report, Hopkins Motor/Vocal Scale	Tourette's Syndrome Study Group 2002 showed a significant treatment effect using the Yale Global Tic Severity Scale (10.9 points, 98.3% CI 2.1 to 19.7; P = 0.003). Singer 1995 found no significant difference on measures of tic severity.	170 (2 studies)	⊕⊕⊖⊖ **Low**[a]

Guanfacine

One 8 week parallel group trial of guanfacine vs placebo in 34 children

Guanfacine significantly reduced symptoms of ADHD on the ADHD Rating Scale Total Score (teacher) and tics on the YGTSS Total Tic Score

Atomoxetine

Parallel group study of atomoxetine in 148 children for 18 weeks

Primary objective – to test the hypothesis that atomoxetine does not worsen tics in children with TS+ADHD relative to placebo

Significant improvement in ADHD symptoms on the ADHD Rating Scale total score with atomoxetine compared to placebo

Atomoxetine was non-inferior to placebo on the YGTSS total tic score

Tics decreased by 5.5 points in the atomoxetine group and 3 points in the placebo group

Conclusions from systematic review

- Psychostimulants should be considered first line treatment of ADHD in children with tics
- More evidence to support use of methylphenidate than dextroamphetamine
- Lowest effective dose should be used as dose of methylphenidate in studies was at lower end, and higher doses of dextroamphetamine worsened tics
- If tics are exacerbated by psychostimulants, evidence to support the use of clonidine and guanfacine for ADHD and tic symptoms, and atomoxetine for ADHD symptoms


OCD
OBSESSIVE–COMPULSIVE DISORDER

DSM V Criteria for OCD

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):

1. Recurrent and persistent thoughts, urges, or impulses that are experienced as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.

2.The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):

1. Repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.

2.The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

DSM 5 Criteria for OCD

Note: Young children may not be able to articulate the aims of these behaviors or mental acts.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder

Specify if: tic-related, the individual has a current or past history of a tic disorder

OCD in TS

Tic-related OCD may differ from pure OCD; inconsistencies reported across studies

Tic-related OCD has an earlier age of onset and is more common in males

Patients with tic-related OCD have higher rates of ADHD, autistic traits, other disruptive behaviour disorders, trichotillomania, and body dysmorphic disorder than patients with OCD without tics

May have different types of OCD symptoms

May have more aggressive, sexual, religious and symmetry related obsessions

More counting, ordering, touching, blinking, hoarding and self-damaging compulsions

Tourettic OCD

Intermediate phenotype

Symptoms are influenced by features of both OCD and TS and differ from either disorder alone

Patients present with thoughts, sensations, and behavioural urges at the interface of compulsions and tics

Rather than describing obsessional thoughts, patients describe a feeling of intense physical discomfort that drives compulsive behaviours

The sensation can become intolerable and anxiety provoking if not mitigated by engaging in the desired behaviour

Compulsions consist of complex motor acts such as touching or tapping in a specific way, vocalizing phrases, or a multistep progression of movements and vocalizations

Compulsions often need to be repeated multiple times until they feel “just right”

Recent review: Katz 2022 Frontiers in Psychiatry

“Pure O” OCD

“Purely obsessional” OCD

2% of people with OCD

Describes OCD phenotype in which visually obvious compulsions are absent

Taboo or unacceptable thoughts

Patients with Pure O engage in mental rituals that are unseen

- Mentally reviewing memories or information
- Mentally repeating words
- Mentally undoing and redoing actions
- Compulsive reassurance seeking

Treatment of OCD in TS

First line treatment of OCD in individuals with (or without) tics should be cognitive behavioural therapy

One RCT (POTS1) suggested that individuals with tics may not respond as well as those without tics to SSRIs for OCD symptoms

Meta-analysis of 20 RCTs of CBT and SSRIs for pediatric OCD found that tic-related OCD moderates CBT efficacy, suggesting that youth with tic disorders may be more responsive to CBT

Treatment of OCD

Effect size greater for CBT than SSRIs for treatment of OCD in children

Systematic review and meta-analysis (McGuire 2015)

CBT

Hedge's g = 1.21, 95% CI 0.83-1.59, NNT = 3

SSRI monotherapy

Hedge's g = 0.50, 95% CI 0.37-0.63, NNT = 5

POTS-I

Pediatric OCD Treatment Study

RCT of 112 youth ages 7-17 years with OCD

Randomized to sertraline, CBT, combined sertraline plus CBT, or placebo

All 3 active treatments were superior to placebo

Combined treatment superior to either treatment alone

CBT and sertraline alone did not differ for reducing symptom severity

For remission, combined treatment and CBT alone did not differ and both outperformed sertraline alone

POTS-II

RCT of 124 youth 7-17 years with OCD

Examined efficacy of CBT augmentation strategies in those with a partial response to optimal SSRI treatment

Participants randomized to (1) medication management, (2) medication management plus CBT augmentation, or (3) medication management plus instruction in CBT skills

POTS-II

Participants who received medication management plus CBT augmentation had significantly greater symptoms reduction than the other two groups

66 of 124 (53%) had tic-related OCD, suggesting a partial response to optimal SSRI treatment may be more common in this subgroup

SSRIs for OCD

Trials of fluoxetine, fluvoxamine, paroxetine and sertraline suggest similar efficacy

Effect size for clomipramine appears larger than SSRIs

Not used first line because of adverse effects and possible cardiac arrhythmias

Antipsychotic augmentation in OCD

Augmentation of SSRIs with antipsychotics is used in people with treatment resistant OCD

Randomized controlled trials of several antipsychotics vs placebo, added to SSRI treatment

All trials in adults

Hedges' g

Risperidone -0.59 (-1.06, -0.11)

Aripiprazole -1.35 (-1.95, -0.75)

Haloperidol –0.82 (-1.51, -0.14)

Dold et al, International Journal of Neuropsychopharmacology 2015

Antipsychotic augmentation of SSRIs in resistant tic-related OCD in children & youth

Naturalistic study of 120 patients (7-18 years) with tic-related OCD

Treated with SSRI monotherapy for 12 weeks; non-responders (n=69) received augmentation with risperidone or aripiprazole for 12 weeks

39/69 had clinically important improvement in OCD symptoms with antipsychotic augmentation

47/69 experienced improvement in tics

Treatment of tic-related OCD

Based on available evidence

Give high priority to CBT as initial treatment

Patients who do not demonstrate adequate improvement with CBT alone should go on to pharmacotherapy with an SSRI, using doses at the higher end of the recommended range and waiting at least 12 weeks for a treatment response

In treatment refractory patients, antipsychotic augmentation can be considered

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