Tourette's & OCD:
Treatment of Comorbid Conditions

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Patients with TS are at increased risk for a number of behavioral and psychosocial problems, including:

- Attention Deficit/Hyperactivity Disorder
- Obsessive Compulsive Disorder
- Anxiety disorders
- Mood disorders and risk of suicide
- Disruptive behaviors
- Learning disabilities and poor school performance
- Sleep disorders

Treatment of ADHD in Children With Tourette's syndrome

- Case reports over the past three decades suggest that stimulants may induce the emergence of tics or an increase in preexisting tics in children with ADHD.
- Two placebo-controlled trials (1992) also reported the emergence of tics in a small percentage of children treated with stimulants.
- This body of evidence has had an enormous impact on clinical practice until recently.

- Over the past decade, three short-term, placebo-controlled studies reported no significant increase in tics among stimulant-treated subjects compared with placebo.

- Two naturalistic studies also provide information on the longer-term effects of stimulants in children with TS.

TACT study

In the 16-week Treatment of ADHD in Children With Tic Disorders (TACT) trial conducted by the Tourette Syndrome Study Group (2002), 136 children with ADHD and a tic disorder were randomly assigned to:

- Placebo
- Clonidine alone
- Methylphenidate alone
- Clonidine plus methylphenidate

- Although the effect was modest, tics declined in all active treatment groups.
- Compared with doses given in the MTA study, the dose of methylphenidate in the TACT study was relatively low in this study
- Taken together, the results of the TACT trial indicate that methylphenidate can be used safely in children with TS.

- A meta-analysis found that methylphenidate did not worsen tic severity among four placebo-controlled randomized trials involving 191 subjects with both TS and ADHD.

- In addition, a meta-analysis of 22 studies involving 2385 children with ADHD and no tic disorder at baseline found that psychostimulant treatment compared with placebo did not increase the risk of new-onset or worsening tics

- These findings suggest that stimulants should be considered in the treatment of children with ADHD and tics.

Treatment of Tourette's in children with ADHD

- Medication options that treat both tics and ADHD include the alpha adrenergic agonists guanfacine and clonidine.

- When central nervous system (CNS) stimulants are required to control ADHD symptoms in the setting of tics, some experts prefer to treat the tics first with antidopaminergic drugs before initiating CNS stimulants.

- Other experts prefer to start treatment for ADHD and closely follow tic severity.

Nonstimulants

A range of nonstimulant medications have been used in the treatment of children with ADHD, including:

- Selective noradrenergic reuptake inhibitors (Atomoxetine)
- The novel antidepressants (Bupropion)
- Alpha adrenergic agonists (Clonidine, Guanfacine)
- Modafinil
- Selegiline

Atomoxetine

An 18-week, placebo-controlled study by Allen et al. (2005) evaluated the efficacy and safety of atomoxetine in 148 children (mean age=11.2 years) with ADHD and a chronic tic disorder:

- Atomoxetine showed a 28% improvement on a clinician-rated measure of ADHD symptoms compared with 14% for placebo.

- We find atomoxetine, a non-stimulator, only modestly effective in the treatment of TS-related ADHD.

Selegiline

Selegiline is a selective MAOI that directly enhances dopamine function in the brain.

It is metabolized to an amphetamine compound in the brain, which may enhance central catecholamine function.

Feiginet al. (1996) studied selegiline in children with TS and ADHD:

- Overall, selegiline was no better than placebo.
- There was no apparent impact of selegiline on tics.

Alpha adrenergic agonists

- Guanfacine and clonidine are effective for treating the symptoms of ADHD and may be helpful in patients with TS who have ADHD or predominant behavioral symptoms, particularly impulse control problems and rage attacks.

- Data from randomized trials suggest that clonidine and guanfacine are useful for suppressing tics but the evidence for tic reduction with these agents is not consistent.

- In some trials, alpha adrenergic agonists were no better than placebo for reducing tics, and indirect evidence suggests that the magnitude of effect may be less than that of the dopamine antagonists.

- A 2019 systematic review concluded that there was moderate confidence that clonidine was more effective for tic reduction compared with placebo.
- There was low confidence that guanfacine was more effective than placebo.
- Although alpha adrenergic agonists are only modestly effective against tics, they are used by some experts as first-line therapy in patients with early or mild tics.

Treatment of OCD in Children With Tourette's Syndrome

OCD & TS

- Most randomized trials of SRIs in children and adolescents with OCD have excluded subjects with TS.
- In addition, there is evidence in children and adults that tic-related OCD may be a distinct subtype of OCD.
- Thus, it is not at all clear that SRIs will be effective in children and adolescents with tic-related OCD.

For children who have TS and mild to moderate OCD, the suggested initial treatment of OCD is:

- cognitive-behavioral therapy.

For more severe presentations of pediatric OCD the suggested treatment involves:

- A combination of cognitive-behavioral therapy and a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine.

- Some tics are associated with an intense urge to perform the movement and are sometimes referred to as "compulsive tics."
- These tics may improve with CBIT* but often need to be treated as compulsions with SSRIs.
- Patients who do not respond to these measures can be treated with second-generation antipsychotic drugs.

*Comprehensive Behavioral Intervention for Tics.

OCD Comorbidities

More than half of pediatric patients with OCD have been found to have at least one comorbid psychiatric disorder

- Any psychiatric disorder, 63 to 97 percent
- Mood disorder, 13 to 70 percent
- Anxiety disorder, 13 to 70 percent
- Disruptive behavior disorder, 3 to 57 percent
- Tic disorder/Tourette's syndrome, 13 to 26 percent
- Speech/developmental disorders, 13 to 27 percent
- Enuresis, 7 to 37 percent
- Pervasive developmental disorder, 3 to 7 percent
- Eating disorders, particularly in adolescents

- Co-occurring mood disorders and psychosis have increased prevalence in adolescents with OCD.

- co-occurring ADHD and anxiety disorders have been found to occur at higher rates in children with an early age of onset of OCD.

Drug Interaction Management

Methylphenidate

Clonidine

- More recent studies have evaluated the safety of combined clonidine and methylphenidate in randomized, double-blind trials of moderate size (n=122-136).

- From these, no evidence of adverse cardiovascular or other events have been reported, leading the authors to conclude that such a combination is safe

Methylphenidate

Antipsychotic agents

- Methylphenidate prescribing information cautions that the impact of methylphenidate on dopamine signaling (inhibition of dopamine reuptake) may result in an interaction with dopamine antagonists such as the antipsychotics.

QTc prolonging agents

QT-prolonging Agents (Moderate Risk) Interacting Members:

Pimozide, Citalopram, Clozapine, Doxepin, Escitalopram, Flupentixol, Olanzapine, Quetiapine, Risperidone, Thioridazine

QT-prolonging Agents (Indeterminate Risk - Caution) Interacting Members:

Amitriptyline, Atomoxetine, Donepezil, Fluoxetine, Fluphenazine, Hydroxyzine, Lithium, Mirtazapine, Sertraline, Trazodone,

Pimozide
(QTc-Prolonging effect)

Fluoxetine or Paroxetine

- Fluoxetine may enhance the QTc-prolonging effect of Pimozide.
- Fluoxetine may increase the serum concentration of Pimozide.

- The mechanism for this apparent interaction is described as being inhibition of the CYP2D6-mediated metabolism of pimozide by paroxetine.

- The fluoxetine prescribing information also specifically contraindicates concurrent use with pimozide due to the potential for fluoxetine to inhibit the CYP2D6-mediated metabolism of pimozide and to increase the potential for QT interval prolongation.

Fluoxetine, Paroxetine, Bupropion,
(Strong CYP2D6 inhibitors)

Haloperidol

- The haloperidol prescribing information states that CYP2D6 inhibitors may increase haloperidol concentrations which increases the risk for adverse events, including QT prolongation.

  The mechanism of this interaction is due to CYP2D6, an enzyme partially responsible for haloperidol metabolism.

Fluoxetine, Paroxetine, Bupropion,
(Strong CYP2D6 inhibitors)

Risperidone

- The dose of risperidone should be evaluated and likely adjusted when combined with strong CYP2D6 inhibitors.
- The dose of risperidone should not exceed 8 mg per day when combined with strong CYP2D6 inhibitors.

Fluoxetine, Paroxetine, Bupropion,
(Strong CYP2D6 inhibitors)

Aripiprazole

- Decrease the aripiprazole dose to 50% of the usual dose when initiating concomitant therapy with a strong CYP2D6 inhibitor, and further to 25% of the usual dose in patients who are also receiving strong CYP3A4 inhibitors.

Lithium

Fluoxetine and clomipramine

- Serotonergic Agents may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors.
- This could result in serotonin syndrome.