Complex Tics and Complex Management in a Case of Severe Tourette’s Disorder (TD) in an Adolescent

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Chief Complaint and Presenting Problem

S. is a 16-year-old adolescent boy with Tourette’s Disorder (TD) referred to our clinic through family friends. The parents reported that S. was currently hospitalized for severe tics at a medical center. They were seeking additional consultation and follow-up treatment.

History of Present Illness

The parents reported that S. had low-pitched vocalizations since about age 3 or 4 years. The parents report that they consulted their pediatrician who said that S. would “outgrow” the sounds. S. subsequently went on to develop complex finger movements and some intermittent throat clearing. At no time did these sounds or movements cause distress or interfere with S.’s functioning in any way. However, in the summer when S. was 13 years old, he developed the onset of forceful mouth opening movements. The parents report that there were no unusual stresses, illnesses, or changes in S.’s life at that time. The forcefulness of the mouth opening gradually increased, and S. subsequently developed episodes in which he would “space out.” The parents reported that there were times when S. would not remember things that had happened. On occasion, S. would fall and then complain that he did not know how he got from one place to the other. Additionally, in the year prior to presentation, S. reportedly had a seizure and fell off a gas scooter, losing consciousness and fracturing an arm. S. had been wearing a helmet and did not experience head trauma, but reported that he “blacked out” while riding the scooter, leading to the crash. S. was hospitalized and underwent a 72-hour video EEG, which showed no seizure activity. He was also evaluated by a pediatric neurologist who recommended an empiric trial of oxcarbazepine, even though there were no seizures observed during the video EEG. A cardiac workup was normal, including normal EKG and echocardiogram.

The parents reported that immediately after the oxcarbazepine was begun, S.’s tics increased significantly, including much more forceful mouth opening, arm and shoulder movements, and head and neck movements. He had a primary complex tic that comprised of a sequence of both motor and vocal tics, beginning with a premonitory sensation of general overall tension, leading to an urge to stretch his neck. After stretching his neck and throwing his head backwards, the tic included mouth opening, muscle stretching in his upper body, fist clenching, feet stretching, and rubbing his face. During this time, the vocal component included cursing with the “F” word followed by throat clearing, squeaking, and a “sh” sound. When asked about potential precipitants of the tics, S. readily reported that stress was a trigger.

S. was taken off oxcarbazepine and switched to levetiracetam, which also did not seem helpful as the movements continued to worsen. S. was evaluated by another neurologist who reportedly recommended discontinuation of the levetiracetam and another outpatient video EEG, which again revealed no seizure activity. S. was subsequently treated with clonidine, clonazepam, and guanfacine, all of which were not helpful as per mother.

Through family friends, S. was referred to a movement disorder specialist. At that time, S. was diagnosed with Tourette’s Disorder (TD), and treatment was started with risperidone and benzotropine. For approximately five months, S.’s tics essentially remitted. However, he gained a significant amount of weight during this time. He also became depressed, lethargic, and developed suicidal ideation, according to his parents, but did not actually try to act on the suicidal thoughts or harm himself.

During the several months prior to presentation to our clinic, parents reported that S. had only occasional head and neck thrusts and occasional coprolalia, but not nearly to the degree that he had these symptoms in the previous six months. During this time, S. was referred to a child and adolescent psychiatrist who diagnosed anxiety. S. was started on fluoxetine, which was gradually increased to his current dose of 30 mg. Parents report that this has been helpful for him.

S. asked to go off the risperidone two months prior to presentation to our clinic because of mood problems and weight gain. According to his parents, the medication was tapered and discontinued, and S.’s tics gradually got worse in one month prior to presentation. The head and neck thrusting movements increased, and S. reportedly developed a rotatory component. In an attempt to switch to a medication with less weight-gain potential, ziprasidone was prescribed up to 80 mg twice a day (bid) for about a month, with very little
beneficial effect. Approximately two weeks prior to S.’s admission to the hospital, aripiprazole 10 mg bid was started. Topiramate was added to help reduce appetite and to facilitate weight control.

S. continued to have very intense tics despite the medication changes. Ten days prior to his admission to the hospital, S. developed extremely loud screams and use of the “f-word.” H also had such severe head and neck thrusts that his mother thought he would “break his neck.” During a car ride, S. reportedly screamed that he “cannot stand it any more,” and began to make an effort to jump out of the car. His mother reports that S. had been having complex tics that “start at the top of his head and go to the whole body” and that last for 5–12 minutes. S. was also beginning to feel that he had to do this complex movement four times in a row, and would sometimes hold his breath during this tic.

S. was admitted to the inpatient neurology service at a medical center one week prior to his presentation to our clinic. While in the hospital, S. was given diphenhydramine, diazepam, and lorazepam intramuscularly to attempt to control the tics; he was then switched to midazolam IV to induce a coma to “break the tic episode.” S. was also given zolpidem and alprazolam. Parents report that the dose of midazolam had been reduced over the past week, but S. then appeared very groggy and continued to have tics. The only time he had not had tics was during sleep. Medications while in the hospital included: doxycycline sodium 100 mg by mouth (PO) every 12 hours (q12h), fluoxetine 30 mg by PO daily, methylprednisolone injection for three days, I.V. midazolam injection and I.V. ranitidine HCL injection 50 mg every 8 hours (q8h), risperidone 0.5 mg daily, topiramate 50 mg q12h, and zolpidem 10 mg q12h.

Repeat video EEG was described as within normal limits. MRI and CAT scan done over the course of the past six months were also described as within normal limits. Mother reported that blood work showed no streptococcus infection and normal copper and ceruloplasmin levels.

While in the hospital, S. was restarted on risperidone 5 mg with the plan to increase it as tolerated. During the course of the hospitalization, the length and intensity of each tic episode somewhat diminished. S. still had some episodes in which he seemed to “collapse” and questionably lose consciousness during head rotations. He was placed on an acute course of steroid therapy. S. was discharged from the inpatient neurology service on risperidone 5 mg, fluoxetine 30 mg, benztrpine 0.5 mg bid, topiramate 50 mg bid, zolpidem 10 mg daily, and alprazolam 0.25 mg in the evening (reduced from 0.25 mg bid). Mother reported that she also added fish oil 1000 mg twice daily in the several days prior to presentation to our clinic, and the alprazolam was discontinued.

S. and his mother reported on presentation to our clinic that the complex tics had reduced in frequency, duration, and intensity since hospitalization.

With regard to anxiety symptoms, parents report that S. has been “a little worrier” all of his life. He became more anxious when he made the transition from elementary school to middle school. Parents report that he “withdrew from friends,” lost interest in things, and “drew into himself” when he started eighth grade. S. often complained of hating school in eighth, ninth, and tenth grades, and often did not want to go to school. Mother reports that since the beginning of tenth grade S. “begged to stay home,” although this was likely related to his increase in tics. S. has been home-schooled since November of tenth grade, 8 months prior to presentation at our clinic, due to the severity of his tics. S. acknowledged that he worried about school and his performance there.

Mother reports that S. has also had some obsessive-compulsive symptoms. Parents report that S. counts excessively and does things in certain numbers, such as four tics in a row. He orders and arranges things excessively. There have been no excessive worry about germs, bad things happening to his parents, or other catastrophic thinking or intrusive thoughts. There have been no history of panic attacks or phobic symptoms. There is no history of hyperactivity, impulsivity or short attention span. Behavior was reported to have always been exemplary. S. is described as having a short fuse, typical of an adolescent, but has had no significant problems with anger control. There was no history of significant elevation of mood, giddiness, silliness, racing thoughts, or need for less sleep.

Past Psychiatric History
There is no other past psychiatry history, and S. had not had behavioral treatment of tics.

Developmental History, Including Pregnancy, Birth, and Infancy
S. is the product of a 40-week pregnancy complicated by swollen ankles. S. was born vaginally with a birth weight of 8 pounds. The newborn period was uncomplicated, and there were no early neonatal problems. Developmental milestones were described as within normal limits for motor, language, and adaptive development.

Educational History
S. attended public schools throughout his life and had just completed tenth grade at a public high school. S. was described as a straight A student who was home schooled this past year due to severe tics. Parents report that S. did not receive any accommodations during tenth grade despite his severe tics.

Social History
S. was described as interested in acting and theatre in the past, which he gave up with the transition to high school. He was reported to enjoy swimming, water sports and fishing, which he does with his father. S. was reported to have several very good friends, who have been supportive of him during this past year.

Family History
S. lives with his parents and an older sister. The mother and father are both in their forties. The mother reports a history of bipolar disorder type I in the paternal great aunt, treated for many years with valproic acid.

Medical History
S. had two concussions within six months of each other in the past two years while engaged in sports activity. He was
evaluated and found to have no sequelae. For the first concussion, MRI or CAT scan was normal. For the second, S. was hospitalized after his reported seizure and broken arm. Otherwise, there has been no history of surgery or chronic medical illnesses including thyroid, cardiac, asthma, or diabetes. S. has no allergies.

S. eats a typical adolescent diet and has recently started an exercise program. He was described as having grown 12 inches and gained significant weight between ninth and tenth grade, but gained much more weight in the past six months when he was treated with risperidone.

S. is described as an adolescent who sleeps generally soundly but has had some episodes of sleepwalking. He is also described as a restless sleeper who kicks the blankets and sheets off the bed at night.

Medication History

S. had been treated with numerous medications, although for relatively brief durations, including oxcarbazepine, levetiracetam, clonidine, clonazepam, guanfacine, haloperidol and tetrabenazine. He reportedly became “stiff” on haloperidol; a trial of tetrabenazine six months prior to presentation at a maximum dose of 37.5 mg bid resulted in severe depression with suicidal ideation, although S. was not treated at the time with an antidepressant. Risperidone treatment was effective but complicated by lethargy, weight gain, elevated prolactin (up to 65 ng/mL resulting in galactorrhea), and depression. S. was treated for three to four days with olanzapine, and then for one to two weeks with aripiprazole 10 mg bid. with little effect. Fluoxetine was added to the risperidone prior to presentation; this was reported to be beneficial for S.’s anxiety and mood symptoms.

Medications on Presentation to the Clinic

Risperidone 5 mg by mouth daily; fluoxetine 40 mg daily; benzotropine 0.5 mg bid; topiramate 50 mg bid; fish oil 1000 mg bid.

Mental Status Examination on Presentation to the Clinic

S. was evaluated with his mother and grandfather in the room. He was a tall, muscular, casually but neatly dressed adolescent with glasses who looked his appropriate age of 16. S. was generally pleasant and cooperative. He appeared a bit sedated with mild bradykinesia. The conversation was uninterrupted until S. had an episode of unresponsiveness when the discussion centered on the phenomenon of tics. At this point, S. stared off into space for approximately 1–2 minutes, not responding to mother’s questions. After approximately 2 minutes, S. resumed the conversation but could not elaborate on his experience during the interruption. He denied current depressed mood, and his affect was reactive. He denied suicidal or homicidal ideation and further denied any perceptual disturbance, including no auditory or visual hallucinations. His thought process was linear, and his thought content was as described above with no obvious delusions.

After about one hour, S. experienced one tic episode, lasting for about 5 minutes. The episode was begun by interruption of conversation, following by a backward dystonic type neck arch. S. thrust his head backward, clenched his fists bilaterally, and stretched both of his legs out. He then began to open his mouth forcefully, followed by forced vocalizations of the “F” word at a fairly loud pitch on a scale of 3–4. After the “F” word, he made other vocalizations that ended in a “sh” sound. At the end of the sequence, he squeezed both cheeks with each hand rather intensely. There was no self-injurious behavior during this tic episode. S. attempted to take deep breaths during the episode upon advice to try to relax. S. relaxed and resumed normal discussion after the 5 minute episode. He did acknowledge having had the premonitory experience of feeling tension build up within him before the tic sequence.

Rating Scales

The Yale Global Tic Severity Scale (YGTSS) was administered at the time of presentation. S.’s total tic score was 40, with 20 on motor tics and 20 on vocal tics, with an overall impairment rating of 50, given his home-schooling and recent hospitalization due to the severity of his tics.

Brief Formulation

In summary, S. is a 16-year-old adolescent boy referred by his parents for a history of severe TD requiring hospitalization to manage his tics. By history, he also appeared to meet criteria for obsessive-compulsive disorder (full or sub-threshold), generalized anxiety disorder, and a major depressive episode concurrent with risperidone. It also appeared possible, if not likely, that S. experienced a depressive reaction or a major depressive episode in the past during his transition to middle school. Family history contributed a diathesis for TD, in that there is a history of possible obsessive-compulsive symptoms and affective disorder on the maternal pedigree. Medical history contributed a clinical diagnosis of seizure disorder, which resulted in an arm fracture; there is also a significant history of concussion twice in the past two years. It is possible, if not likely, that either or both of these central nervous system disorders were contributing to the severity of the current picture. From a developmental perspective, S. was on a healthy trajectory until the beginning of middle school and the transition to early adolescence, during which he may have experienced increased anxiety and possible mood difficulty. By history, he has had extreme functional impairment secondary to tics in the past year. On the positive side, S. has considerable strengths including excellent academic performance, capacity for warm object relationships, and supportive and resourceful parents who are seeking to optimize his care.

Multi-Axial Diagnoses

Axis I:
- Tourette’s Disorder, severe to marked.
- Obsessive-compulsive disorder, sub-threshold.
- Generalized anxiety disorder.
- Major depressive episode, secondary to risperidone and tetrabenazine, past.

Axis II:
- Deferred.

Axis III:
- Seizure disorder, not otherwise specified.
- Concussion twice within the past two years. Fractured arm, past.

Axis IV:
- Level of psychosocial stressors: Severe: Hospitalized for tics and unable to attend the school in the past year.

Follow Up Outpatient Treatment Course

This is a summary of approximately one year of outpatient treatment since S.’s presentation to our clinic. Initial recommendations included behavioral, psychosocial, and pharmacologic interventions, each of which will be summarized below.

Behavioral treatment

The behavioral component included a referral for habit reversal training (HRT). S. attended several session of HRT initially, and the therapy was effective for identification of his premonitory urges and substitution of a competing response for his simple motor tics. However, it was not possible for S. to extend these results to his complex tics that lasted 5–12 (or longer) minutes in duration. S. discontinued HRT after four sessions, as he and his parents were not convinced that it would be helpful for his complex tics. Many months later, the parents reported that his complex major tic could be stopped at the outset with tickling of S. by one of them. However, S.’s parents were concerned that tickling was only delaying and then increasing the duration and intensity of what seemed to be the inevitable major complex tic.

Psychosocial treatment

The major psychosocial intervention was to enroll S. in a private school with very supportive staff and a small classroom with other children with medical and/or neurologic issues. After several years of enduring bullying and teasing in public school, S. began to like school again, as evidenced by his desire to go to school and an observable improvement in his grades. Psychoeducation, including referral to the Tourette Syndrome Association, and support for the family and S. was also helpful.

Pharmacologic treatment

The family and S. were very concerned about weight gain and galactorrhea, likely from risperidone. After extensive discussions with S. and his parents, it was decided to attempt to cross-taper S. from risperidone to fluphenazine in 1 milligram increments, as S. had never had a trial with pimozide or fluphenazine. This was initially successful, and S. tolerated fluphenazine. The tics did not worsen as fluphenazine was increased to 3 mg total daily and risperidone decreased to 2 mg total daily. However, upon decreasing the risperidone to 1 mg and increasing fluphenazine to 4 mg daily in the fourth week of the cross-taper, S. had an exacerbation of tics. He had been previously hospitalized when risperidone was reduced below 2 mg daily, and this was therefore the second exacerbation of his tics with a decrease in risperidone below a 2 mg threshold. Subsequently, risperidone was restored to 2 mg daily, and fluphenazine decreased back to 3 mg daily, with resolution of the tic exacerbation. S. remained stable on these two medications for approximately four months; his prolactin levels were noted to decrease slightly from 65 ng/mL to 45 ng/mL, although he continued to have mild galactorrhea and weight gain. He had one spontaneous episode of depression with tearfulness and hopeless feelings, with no suicidal ideation, approximately five months after starting treatment. This prompted an increase in his fluoxetine to 50 mg daily with good effect. There was also one spontaneous episode of urinary retention that resolved naturally but prompted reduction of his benzotropine to 0.5 mg daily.

Weight gain was an ongoing problem during the course of outpatient treatment, although lipid and glucose profiles remained in the normal range. Diet and exercise were encouraged at every visit, and the parents and S. tried various diets. Exercise was usually difficult to do for S. as he was sedated on medication and had to be accompanied by his parents or school staff at all times. About four months into outpatient treatment, topiramate was increased for further appetite suppression. This was helpful in terms of suppressing his appetite; however, S. had a tic exacerbation that the parents felt was associated with the increase of topiramate to 75 mg bid. Topiramate was discontinued, despite the treatment team’s opinion that there was a favorable benefit risk ratio. Through the course of outpatient treatment, S. experienced a total weight gain of 50 pounds. Other options are under consideration.

After approximately seven months of outpatient treatment, S. had a spontaneous worsening of tic symptoms with no apparent precipitant and no change in his medications. S.’s major complex tic increased to 6–14 minutes, and began to occur 2–5 times daily. New self-injurious tics emerged, involving hitting himself in the chest and head with his hands bilaterally. Initially, this tic exacerbation was managed with addition of clonazepam 0.5 mg bid–tid, and with increase of fluphenazine to 2 mg AM and 3 mg PM, and risperidone 1 mg bid. S. and his parents were reluctant to increase the risperidone because S.’s tics continued to worsen, and he continued to gain weight. It was still theoretically possible to increase the fluphenazine to even higher doses; however, the parents and S. were very distraught about his tics. They began to inquire about surgical options for the treatment of TD, including deep brain stimulation, which is indicated only for adults with treatment refractory illness (Larson 2008). It was felt that S. was not treatment-refractory at that time, as he had not yet had a trial of pimozide or some other medication interventions.

A pimozide trial was begun cautiously in one mg incrementations per week with weekly EKG monitoring, as S. was concurrently taking fluoxetine 50 mg daily. Pimozide is metabolized primarily by CYP 450 3A4, so it was expected that its concentration would be elevated, with potential increase in QTc interval, due to inhibition of its hepatic metabolism by fluoxetine. In the first two weeks following the addition of pimozide, there was no benefit and no QTc prolongation noted. However, S.’s tics were worsening, so it was decided to hospitalize him due to his severe and self-injurious tics and to more quickly increase the pimozide in a monitored setting. Clonazepam was also increased to 0.5 mg daily. On admission, S.’s QTc was in the normal range, but after increasing the pimozide to 3 mg total daily (and decreasing the fluphenazine to 1 mg by mouth in the morning and 3 mg by mouth in the evening) S.’s QTc interval increased over two days to 467 msec, beyond the upper limit of normal (450 msec). He was evaluated by cardiology, and it was recommended that the pimozide be discontinued, along with discontinuation of the fluoxetine. The pimozide and fluoxe-
Discussion

The QTc prolongation on pimozide and fluoxetine was noteworthy, and hospitalization was indicated, since clearance is slow for both agents, (Sallee et al. 1987). Fluoxetine is a potent inhibitor of the hepatic enzyme 2D6 and a moderate inhibitor of 3A4 (Caccia 1998). Pimozide is metabolized primarily by 3A4, and plasma levels can be elevated due to inhibition of its hepatic metabolism by fluoxetine. There have been three case reports of sudden death on pimozide when clarithromycin was added, which is a potent inhibitor of 3A4 (Flockhart et al. 2000). There are no case reports of sudden death with pimozide and fluoxetine co-administration; however, there are some reports of adverse cardiac effects with the co-administration of the two drugs (Ahmed et al. 1993; Friedman 1994).

There is otherwise very little literature regarding the co-administration of a selective serotonin reuptake inhibitor (SSRI) with pimozide. One brief report describes 28 patients with body dysmorphic disorder on a mean dose of 62.5 mg/day of fluoxetine assigned to augmentation with either placebo or pimozide (Phillips 2005). Eighteen patients were assigned to take placebos with fluoxetine, and 11 patients to pimozide, which was increased to a dose of 10 mg/day if tolerated (Phillips 2005). There were no reports of any adverse events during the study, although no mention was made of cardiac monitoring.

Given the documented cardiac effects of this combination in outpatient settings (Ahmed et al. 1993; Friedman 1994) and S.’s QTc prolongation observed in the hospital with the co-administration of fluoxetine and pimozide, EKG monitoring is indicated. Fluphenazine and risperidone are also inhibitors at 2D6, but not at 3A4. Citalopram, a mild inhibitor of 2D6, but not of 3A4, could be considered, whereas fluvoxamine, paroxetine, and sertraline, moderate to potent inhibitors of 2D6 and 3A4, could potentially be more risky. British guidelines have a contraindication on the co-administration of 3A4 inhibitors (of any degree). Children should also be advised that grapefruit juice, a moderate inhibitor of 3A4, should not be consumed during treatment with pimozide.

Pimozide-fluoxetine interactions are further complicated by the pharmacokinetics of both drugs. There is extremely slow elimination of fluoxetine and its active metabolite norfluoxetine from the body, which distinguishes them from most other antidepressants. With time, fluoxetine and norfluoxetine inhibit their own metabolism, so fluoxetine elimination half-life changes from 1 to 3 days, after a single dose, to 4 to 6 days, after long-term use. Similarly, the half-life of norfluoxetine is longer (16 days) after long-term use. In one prior study, the mean elimination half-life of pimozide in children was 66 hours compared with 111 hours in adults with TD although there was significant inter-individual variability of pimozide pharmacokinetics in both adults and children with TD (Sallee et al. 1987).

To date, there are no published data on the efficacy of fish oil in the treatment of TD, but a study has recently been completed (Gabbay & Coffey, 2007; Gabbay et al. 2008). More studies are needed.

In summary, S.’s tic symptom severity was profound, and his clinical course and follow-up illustrate some of the challenges of treatment of severe tics in an adolescent. While comprehensive biopsychosocial treatment approaches are aspirated to in all cases, it is not always feasible to combine evidence-based treatments for each individual.
Disclosures

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References


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