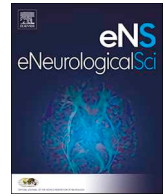




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Case report

## A pediatric neurobehavioral treatment challenge

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### ARTICLE INFO

#### Keywords:

Tourette  
Tourette's syndrome  
Movement disorder  
Tardive dyskinesia  
Tic disorder

### ABSTRACT

Tourette's syndrome (TS) currently has very limited FDA approved treatment options, despite the fact that TS and other pediatric tic disorders are not uncommon and can cause significant emotional and physical distress for patients and their families. For providers who regularly see these conditions in practice this inadequacy is highly frustrating on the treatment side as there are such limited options to offer to these families, and the outcome to hope for is not highly optimistic. The outcome of this case presentation is an example of how health care providers can use clinical knowledge in combination with evidence-based practice to advocate for their patients and find new solutions that could be, and in this case were, life changing. It promotes providers to advocate for their patients and expand their knowledge. The final medication treatment utilized in this case is currently off label, however the method of finding and obtaining the treatment explained in the case additionally reveal to readers how to cautiously but judiciously make off label treatment decisions that can be important to practice and patient outcomes. In the course of this case the off-label medication use decision was backed by scientific literature and ongoing FDA studies as well as consulting with a collaborating psychiatrist. The subject matter and method of reasoning within this case also promote psychiatric providers use of evidence-based practice and implementation of science into active practice.

### 1. Introduction

Tourette's Syndrome (TS) is a common pediatric illness characterized by both multiple motor and one or more vocal tics with an estimated lifetime prevalence of 3 per 1000 individuals [1,2]. Children and adolescents who suffer from TS frequently encounter difficulties with academics as well as family and peer relations [3]. However, the only currently FDA approved medications for TS are haloperidol (approved for pediatric TS in 1978), pimozide (approved for pediatric TS in 1984), and aripiprazole (approved 2014 for pediatric TS but first marked for other indications in 2002) [4]. All three of these medications are in the antipsychotic class, and largely share a theorized primary mechanism of action of blockade of the D<sub>2</sub> dopamine receptor [5]. Antipsychotic medications have various side effects, including Tardive Dyskinesia (TD), a neurological condition which causes involuntary choreoathetoid movements, which can be permanent, and can occur with as little as 3 months of exposure [6]. Prevalence of TD is correlated with age, and in children and adolescents is estimated to be 0.4% [7]. While

other medications are frequently used for treatment of TS, including  $\alpha$ -agonists, such as guanfacine, the effect size of these medications is low to moderate [8,9]. These commonly used  $\alpha$ -agonists can lower blood pressure and cause significant daytime drowsiness or somnolence as common side effect that have to be monitored and can be intolerable to patients.

The sparse offerings of FDA approved treatment options for such a debilitating condition as Tourette's Syndrome coupled with the considerable associated side effects thereof, the recent ongoing clinical trials for selective vesicular monoamine transporter type 2 (VMAT2) inhibitors for TS should be of note to clinicians treating TS [9]. These drugs offer significant symptom improvement, as well as a better side effect profile, but are not utilized by practitioners for TS, due in part to the lack of published studies supporting their use in treating TS [10,11]. This case study presents evidence based clinical support to help fill that gap.

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<https://doi.org/10.1016/j.ensci.2020.100244>

Received 3 January 2020; Received in revised form 21 April 2020; Accepted 18 May 2020

Available online 20 May 2020

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## 2. History

This 11 year old male presents to the visit with a height of 5'1" (90th percentile) and weight of 115 pounds (92nd percentile). He lives with his mother, father and 3 younger siblings. His father is active in the military and has been deployed more than once during the course of this patient's treatment, but is currently living in the home. The family history was significant for ADHD in both parents and one sibling, depression in the mother, Bipolar disorder in an uncle and maternal grandmother, and Tourette's syndrome in an uncle. He was initially evaluated at age 5, and both his parent and teacher histories and Vanderbilt scores confirmed elevated symptoms of impulsivity, hyperactivity and inattention at home and in the classroom settings. This child was experiencing performance struggles in both academics and conduct. These performance difficulties were additionally causing him frustration and emotional distress as he was not making the grades he was capable of, plus he was regularly getting into trouble at school due to his level of impulsivity. At initial evaluation, it was reported that he had a history of a lip smacking tic that had been transient, but currently was not problematic or significantly bothersome for the patient or his parents.

The patient was diagnosed with ADHD- Combined presentation and transient tic of childhood. A stimulant trial was initiated with amphetamine ER 5 mg at initial evaluation based on family history and clinical presentation. This patient had a fairly immediate and significant ADHD symptom improvement, but side effects of both motor and vocal tics were exacerbated, so this medication was discontinued.

Over the course of the next 6 years this young man was followed and treated for ADHD, but his tics persisted even off medications and a diagnosis of Tourette's syndrome was confirmed. At various times throughout his treatment course, his tics were so pronounced he experienced significant anxiety due to his level of awareness of their severity. He also experienced tic movements in his sleep so [he] had difficulty sleeping and would actually wake up complaining of muscle soreness. This boy also began complaining of increased problems with focus in school at times. It was determined that the increasing poor focus was related to his level of distraction caused by his tics not primarily a symptom of his ADHD.

Specialists were consulted at different times during his course of care. An integrative pediatrician also diagnosed and treated him for PANS (pediatric acute onset neuropsychiatric syndrome). A pediatric neurologist evaluated him for treatment options for Tourette's, however, the treatment recommended was clonidine which this patient had already failed previously. This boy was also referred to a behavioral therapist for emotional support and to learn techniques to help distract him from his tics. Working with a therapist provided some benefit for him, but those benefits were primarily emotional and related to his comorbid anxiety. During the six year treatment course for this young boy, many medications were tried and eventually discontinued either because there was no improvement or because of side effects (Table 1). The only medications he tolerated and had any sustained benefit from are atomoxetine 80 mg daily and methylphenidate CD 20 mg daily both for ADHD, and sertraline 150 mg daily for anxiety (which at times helped some with tics also). His co-morbid conditions are allergic rhinitis, asthma (moderate persistent), Methylene tetrahydrofolate reductase (MTHFR) deficiency (Homozygous C677T T/T), COMT polymorphism (Val158Met Met/Met) ADHD, Anxiety, Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). He takes montelukast, levocetirizine, fluticasone/astelazine and albuterol as needed. (Insert Past Medication Trials – Table 1).

He and his mother both reported he was having difficulty with focus at school and his grades are suffering. His tics were worse and he was distressed by his tics and reported embarrassment at how noticeable they were to others. It was also felt that, despite his ADHD being well controlled, he was having difficulty focusing due to his tics, especially in school, and felt his decline in academics may be due to this. The boy

and his mom both endorse that his recent increase in anxiety and irritability seem to correlate to the severity of his tics and his frustration about how he is viewed by others.

An Abnormal Involuntary Movement Scale (AIMS) was completed because of his past history of antipsychotic use, movement reports and observations in the office. His score is a 23. The AIMS is a widely used instrument for evaluating Tardive Dyskinesia (TD) movements and was developed by the Psychopharmacology Research Branch of the National Institute of Mental Health [6,14]. The breakdown of this instrument includes severity ratings for body movements by area categories as well as ratings for overall severity of the movements and the patient's self-reported level of distress from their movements. During the initial evaluation of this patient he was having movements during his sleep and self-rated his level of distress as severe. The observed overall severity was rated as severe and incapacitation as mild during the visit. Observed movements on the initial scoring included truncal movements of twisting and squirming were rated as severe. His facial expression movements of blinking, grimacing, eye rolling, jaw clenching, mouth opening and eyebrow lifting which were rated as moderate in severity. His lower extremity movements of knee movements, foot squirming, and upper body irregular arm movements were rated as mild. The tic/movement severity and how this physically and emotionally impacts this patient appears to be causing his inattention in school, increased anxiety, and now additionally irritability and poor academics.

## 3. Physical exam

His physical exam and neurological exam are normal other than observed tics which include eye rolling, jaw/mouth opening, blinking, tongue thrusting, shoulder shrugging, making sounds/noises, and body/trunk jerking.

## 4. Diagnoses

Tourette's Syndrome- severe, worsening.  
Generalized Anxiety Disorder- moderate, worsening.  
ADHD, combined presentation- stable, well controlled.  
Disordered Sleep- not well controlled.

## 5. Intervention

The patient was experiencing moderate to severe impairments in his academic, social, and emotional life caused by the severity of his tics. He had tried 20 different medications for his symptoms and had been referred to 3 specialists without significant symptom control or improvement that could be obtained and sustained with commonly prescribed medications for TS.

Medications in the class of selective vesicular monoamine transporter type 2 (VMAT2) inhibitors are FDA approved for other hyperkinetic disorders such as Tardive Dyskinesia and Huntington's disease, and tetrabenazine was found effective in two open label trials of TS. Two newer VMAT2 inhibitors, valbenazine (Ingrezza, Neurocrine Biosciences, San Diego, CA, USA) and deutetabenazine (Austedo, Teva Pharmaceuticals, North Wales, PA, USA), are currently undergoing large-scale double-blind placebo controlled clinical trials for treatment of TS [10,11].

There is no study site currently open for new participants or close enough for this boy to enroll. Direct communication with a trusted psychiatrist was initiated as well regarding this child's situation.

This psychiatrist agreed with the proposed plan and recommended valbenazine, and provided information on dosing recommendations, potential side effects, risks versus benefits of off label medication uses and the forms necessary to obtaining this medication.

Dosing, potential side effects, risks versus benefits of off label medication uses, and the difficulty of obtaining this medication that may be encountered were discussed at the visit. In clinical trials in

**Table 1**  
Past Medication Failures.

Medication	Outcome
amphetamine salts XR (Adderall XR)	exacerbated tics, caused irritability; ADHD symptom improvement
dexmethylphenidate XR (Focalin XR)	increased tearfulness; increased anxiety/worries; no ADHD symptom improvement
methylphenidate ER (Ritalin LA)	exacerbated tics; ADHD symptom improvement
clonidine (Catapres)	significant somnolence; no tic improvement
guanfacine (Tenex)	no tic or ADHD symptom improvement
guanfacine ER (Intuniv)	no tic or ADHD symptom improvement
paroxetine (Paxil)	caused irritability
citalopram (Celexa)	suicidal ideations were reported
aripiprazole (Abilify)	tolerated well initially with tic and mood improvement- within 4 months developed aggression
oxycarbazepine (Trileptal)	caused aggression/increased irritability
ziprasidone (Geodon)	initially had improvement in mood and tics- later needed dose titration caused significant increase in anxiety
risperidone (Risperdal)	tolerated well initially with tic and mood improvement but lost efficacy and .pt. developed a Limp with dose increase
hydroxyzine (Vistaril)	helped with sleep onset- discontinued when no longer needed
buspirone (Buspar)	no symptom improvement
amantidine *	initially had improvement in tics and mood but later lost effectiveness
cephalexin (Keflex)	no response
azithromycin (Zithromax)	initial tic improvement but later lost effectiveness
prednisolone (Prednisone)	initial tic improvement but later no effect

\* see reference [15].

adults the medication side effect profile was tolerable with mild somnolence being the predominant side effect [12,13]. The patient and his mother verbalized understanding of everything discussed and wanted to move forward so a prescription for valbenazine 40mg once daily was initiated. After 2 months, and a lengthy prior authorization appeal process, a trial of this medication was finally granted and delivered to the family. A follow up visit was scheduled within 2–3 weeks of starting the medication.

## 6. Follow up

When the patient and his mother returned to the office for another medication follow up visit, he was noted to have no observable tics. He reported that shortly after starting valbenazine, he could sleep through the night, and did not wake up sore for the first time in a long time. He and his mother felt that the tics had almost totally resolved.

An updated AIMS score was 2, improved from the pre-treatment score of 23. This is a 91.3% reduction.

The patient and his mother denied the presence of any side effects. While he continued to have some focus and anxiety concerns, they felt that with the reduction in tics they were starting to see improvements in his overall mood and demeanor.

## 7. Conclusion

The paucity of FDA approved treatment options for such an emotionally and socially debilitating condition like Tourette's Syndrome currently leaves much room for advancement in the field of medicine. This case was not only challenging because of the patient's severity of Tourette's symptoms, but also the complexity of his co-morbidities, and prior multiple medication failures and intolerances.

Late-stage trials of both valbenazine and deutetrabenazine, failed to reach statistical significance in separation from placebo, but there was a positive signal that some of the patients achieved a meaningful response with the medications.

For this patient, valbenazine has resulted in a significant improvement in his symptoms, and quality of life, and could potentially do the same for many more children with Tourette's Syndrome and tic disorders in the future.

## Authors statement

Lisa E. Whitley MSN, CPNP, PMHS reports personal fees from Neos

Therapeutics, personal fees from Tris Pharma outside the conduct of this case report.

Craig Chepke, MD, FAPA reports personal fees from Neurocrine Biosciences outside the conduct of this case report, personal fees from Acadia Pharmaceuticals, personal fees from Allergan, plc, personal fees from Ironshore Pharmaceuticals, personal fees from Myriad Genetics, personal fees from Otsuka/Lundbeck Pharmaceuticals, personal fees from Takeda/Lundbeck Pharmaceuticals, outside the submitted work; There were no funding source(s) with any influence or involvement in any aspect of this case report.

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