

Aggressive Symptoms in Children with Tourette Syndrome

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HULK



"Don't make me angry. You wouldn't like me when i'm angry"

Aggressive Symptoms in TS

Overview:

- Phenomenology & classifications of aggressive symptoms
- Causes of aggressive symptoms
- Treatment of Impulsive Aggression (IA) in TS
- Future Directions

Adaptive Aggression

Aggressive behaviors observed in animals

- Dominance behaviors
- Territorial Aggression
- “Female” Aggression

Developmental Aggression

“Temper Tantrums”

- Occurs < 1/3 children ages 3-12 years
- Most common: ages 3-5 years (75%)
- Least common: ages 9-23 (4%)
- More common: boys > girls (3:1)
- Hx: trauma, seizure, tics*, hyperactivity, bedwetting, head banging, sleep problems

(Bhatia et al. 1990)

Temper Tantrums in Preschoolers

279 children ages 3-5 years

- 4 Study Groups: Healthy, MDD, MDD+DR, and DR (ODD/ADHD/CD):
 - MDD+DR (9x), DR (5x) more likely violent/destructive tantrums
 - MDD+DR likely to have longer tantrums
 - MDD + DR most likely to tantrum at home
 - MDD + DR, DR more likely to tantrum at school
 - DR most likely to tantrum outside
 - MDD+ DR most difficulty recovering from tantrum

Duration and Frequency of Tantrums predictive of serious clinical problems

(Belden, Thomson and Luby Pediatric 2008)

Pathological Aggression

Aggressive behavior that is:

- Excessive in intensity, duration, frequency
- Inappropriate to expectable social context
- May be directed toward self, others, objects
- Age-inappropriate

Type of Pathological Aggression

Proactive / Non-impulsive / Predatory

- Onset around age 6.5 years
- Associated with aggressive role models
- Accompanied by *decreased* autonomic activation

Examples: bullying, delinquency/sociopathy

Type of Pathological Aggression

Reactive / Impulsive / “Maladaptive”

- Onset approx. age 4.5 years
- Can be associated with history of abuse/trauma
- Accompanied by *increased* autonomic activation

Examples: “rage attacks”, affective storms

Consensus Report on Impulsive Aggression (IA) in Child Psychiatry

- IA is a meaningful clinical construct
- IA can be reliably measured & appears similarly across diagnostic categories
- IA is informative about illness severity but not type
- Parallel studies of IA across disorders or broad diagnostic criteria can and should be conducted

(Jensen et al. 2007)

Causes of Aggressive Symptoms

- Alcohol/substance abuse
- Medication side effects
- Toxins
- Neurological conditions
- Physical/sexual/emotional abuse
- Pain
- Sleep disorders
- Pre-existing psychopathology

Medication-related Aggression

- Medication-induced activation
- Disinhibition
- Paradoxical reactions
- Behavioral toxicity

Sx: Irritability, anger/rage, excitability
hyperactivity, agitation, mood lability

Causes of Aggressive Symptoms

Medications:

- Alcohol and illicit substances
- Benzodiazepines
- Steroids
- Psychostimulants
- Guanfacine
- Neuroleptics
- SSRIs & other antidepressants *

Causes of Aggressive Symptoms in Adults

Pre-existing psychopathology:

- Antisocial Personality Disorder
- Borderline Personality Disorder
- Major Depression
- Bipolar Disorder
- Schizophrenia
- Attention Deficit Disorder
- Intermittent Explosive Disorder

DSM-IV-TR Diagnostic Criteria for Intermittent Explosive Disorder (IED)

- Discrete episodes of failure to resist aggressive impulses resulting in serious assaultive acts or destruction of property (**Criterion A**)
- Degree of aggression grossly out of proportion to provocation or stressor (**Criterion B**)
- Aggressive episodes not due to direct effects of a substance, other mental disorder, or general medical condition (**Criterion C**)

Prevalence & Correlates of DSM-IV IED

The National Co-morbidity Survey Replication

9282 people ages 18 and older
face-to-face household survey

- Lifetime prevalence: 5.4% - 7.3%
- 12-month prevalence: 2.7% - 3.9%
- Widely distributed in the population
- Usually begins in childhood or adolescence
- Significantly comorbid with mood, anxiety, and substance disorders
- Only 28.8% ever received treatment for their anger

(Kessler et al. 2006)

Causes of Aggressive Symptoms in Children

Pre-existing psychopathology:

- Conduct Disorder
- Oppositional Defiant Disorder
- Major Depression
- Bipolar Disorder, Psychoses
- Attention Deficit Disorder
- Autistic Spectrum Disorders

Instruments for Measuring Impulsive Aggression (IA) across Diagnostic Categories

- The Young Mania Rating Scale
- Parent General Behavior Inventory
- The Aberrant Behavior Checklist
- The Child Behavior Checklist
- Nisonger Child Behavior Rating Form

Neurobiology of Aggression

- DA, opioids, androgens, ACTH facilitate sexual behavior & aggression
- Serotonin (5HT) and NE, possibly via neuromodulators GABA and glutamate mediate inhibitory responses
 - Disturbances of central 5HT linked with aggression and impulsivity
 - Low central 5HT associated with violence
 - Lesions of PFC or OFC linked with aggression

Aggressive Symptoms in TS

- Common in clinical settings
- Impulsive type most typical
- Complex etiology
- Cause severe morbidity
- Treatment still largely non-specific

International TS Database

3,500 TS cases in 22 countries

- 37% anger control problems ever
- 26% anger control problems now
- <10% anger control problems TS only

(Freeman et al.1999)

Explosive Outbursts in TS:

- Abrupt, unpredictable episodes of severe physical and/or verbal aggression
- Grossly out of proportion to any provocation
- Experienced as uncontrollable & distressing
- Accompanied by physiological activation

Clinical Findings: Explosive Outbursts in TS Children

- Explosive Outbursts are symptoms, not a diagnosis
- These symptoms appear unrelated to tic type or severity
- These symptoms appear associated with specific psychiatric disorders, certain current psychotropic usage, environmental factors

(Sukhodolsky et al 2003; Budman et al. 2003, 2000,1998; Stephens and Sandor, 1999)

Treatment of Aggressive Symptoms in Tourette Syndrome

Assessment of Rage Symptoms in TS

Detail the nature of explosive outbursts
in terms of:

- frequency
- severity
- duration
- triggers
- context

Rage Severity Scale

Budman & Coffey (2004)

	0	1	2	3
Frequency (in past week)	None	1-2	3-7	>1 per day
Intensity (most severe of past week)	Absent	Mild (i.e. temper tantrum)	Moderate (i.e. property destruction)	Severe (i.e. requires hospitalization)
Duration (most severe of past week)	None	≤5 min.	6-15 min.	≥16 min.

Total Score:

Mild: 0-3

Moderate: 4-6

Severe: 7-9

Treatment of Rage Symptoms in TS

Comprehensive Evaluation

- **Diagnosis:** medical, psychiatric, neuropsychological
psychosocial assessment
- **Medications:** side effects, drug interactions
- **Psychosocial function:** family, school/work, peers

Treatment of Rage Symptoms in TS

- **Atypical antipsychotics:**
risperidone*, aripiprazole, olanzapine*, ziprasidone, quetiapine
- **SSRIs:**
fluoxetine, sertraline, fluvoxamine, citalopram, paroxetine*
- **Anticonvulsants/Mood Stabilizers:**
Lithium, divalproex, lamotrigine, carbamazepine, topiramate
- **Other:**
psychostimulants, propranolol, clonidine, mecamylamine, EFAs

* published pilot studies in TS

Treatment Recommendations for Use of Atypical Antipsychotics in Aggressive Youths (TRAAY)

1. Treat primary psychiatric disorder first
2. Use monotherapy when possible
3. Employ psychosocial and behavior treatments
4. If/when these initial steps fail, add concurrent atypical antipsychotic

(Pappadopolos et al. 2002)

Case Series: Aripiprazole in Children and Adolescents with Tourette's Disorder with and without Explosive Outbursts

Budman C, Coffey B, Shechter R, Schrock M,
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Background

Aripiprazole:

possible “dopamine-serotonin system stabilizer”

- partial agonist D2 and 5HT1A,
- antagonist 5HT2A
- mild antagonist activities D3, D4, 5HT7, α -1, H1
- may improve cognitive functioning
- antidepressant/anxiolytic effects
- fewer EPS, no effects on prolactin

Background

Aripiprazole: Possible Uses in TS

- **Evidence for tic suppression**
(Robertson 2006; Yoo et al. 2006, Davie et al. 2006; Bubl et al. 2006; Kastrup et al 2005, Murphy et al 2005; Padala et al. 2005)
- **Evidence for anti-aggressive effects in certain psychiatric populations**
(Stachnik et al. 2007; Volavka et al. 2006; Biederman et al. 2005; Stigler et al 2004, Findling 2003)

Objectives

1. To conduct a retrospective, cross-sectional, observational study of aripiprazole for treatment of tics and/or comorbid explosive outbursts in children & adolescents with TS
2. To evaluate tolerability and side effects of aripiprazole treatment in this population

Subjects

- 37 patients with TS (DSM-IV-TR) from a specialty clinic ages 8-18 years who failed to respond and/or were unable to tolerate conventional medications for tics and/or explosive outbursts.
- IRB approval and informed consents were obtained from all patients and their parents/ legal guardians to participate in study
- Known causes of explosive outbursts, major medical or psychotic illness, current conventional or atypical antipsychotic usage and/or prior exposure to aripiprazole were excluded
- No changes permitted in standing psychotropic medications 1 month prior to treatment and throughout 12-week study period

Methods

- 37 children & adolescents with TS (DSM-IV-TR) were treated with aripiprazole for 12 weeks
- Dose initiated at 1.25-2.5 mg daily in pre-pubertal children and 2.5-5.0 mg daily in adolescents
- Dose flexibly titrated every 5-7 days
- 76% (28/37) also taking stable dose concomitant non-neuroleptic psychotropic medications throughout 12-week study

Methods

- Study sample analyzed in terms of:
 - ✓ General clinical characteristics
 - ✓ DSM-IV-TR Psychiatric Comorbidity Status
 - ✓ Current psychotropic medications
 - ✓ Tic ratings at entry and follow-up using CGI-tics
 - ✓ Explosive outbursts ratings at entry and follow-up using CGI-rage
 - ✓ Aripiprazole dosage at study completion
 - ✓ Treatment-emergent side effects

Methods

Assessment of Explosive Outbursts

(DSM-IV-TR diagnosis of IED minus criterion C)

- ≥ 3 episodes/week of sudden, uncontrollable rage characterized by all of the following:
 - Failure to resist aggressive impulses resulting in verbal and/or physical attacks to self or others
 - Behavior is grossly out of proportion to any provocation or frustration
 - Atypical of baseline personality

Methods: CGI Scales (0-6)

CGI-Tics

1. Normal: no tics
2. Borderline: tics may/may not be present
3. Mild: observable tics, but may not be noticeable
4. Moderate: noticeable tics that cause some distress
5. Marked: exaggerated, disruptive tics
6. Severe: extremely disruptive tics, interrupt daily functions

CGI-Rage

1. Normal: no outbursts
2. Borderline: occasional outbursts in past month
3. Mild: >1 explosive outburst in past week
4. Moderate: 2-3 explosive outbursts/week
5. Marked: 4-5 explosive outbursts/week
6. Severe: at least daily explosive outbursts

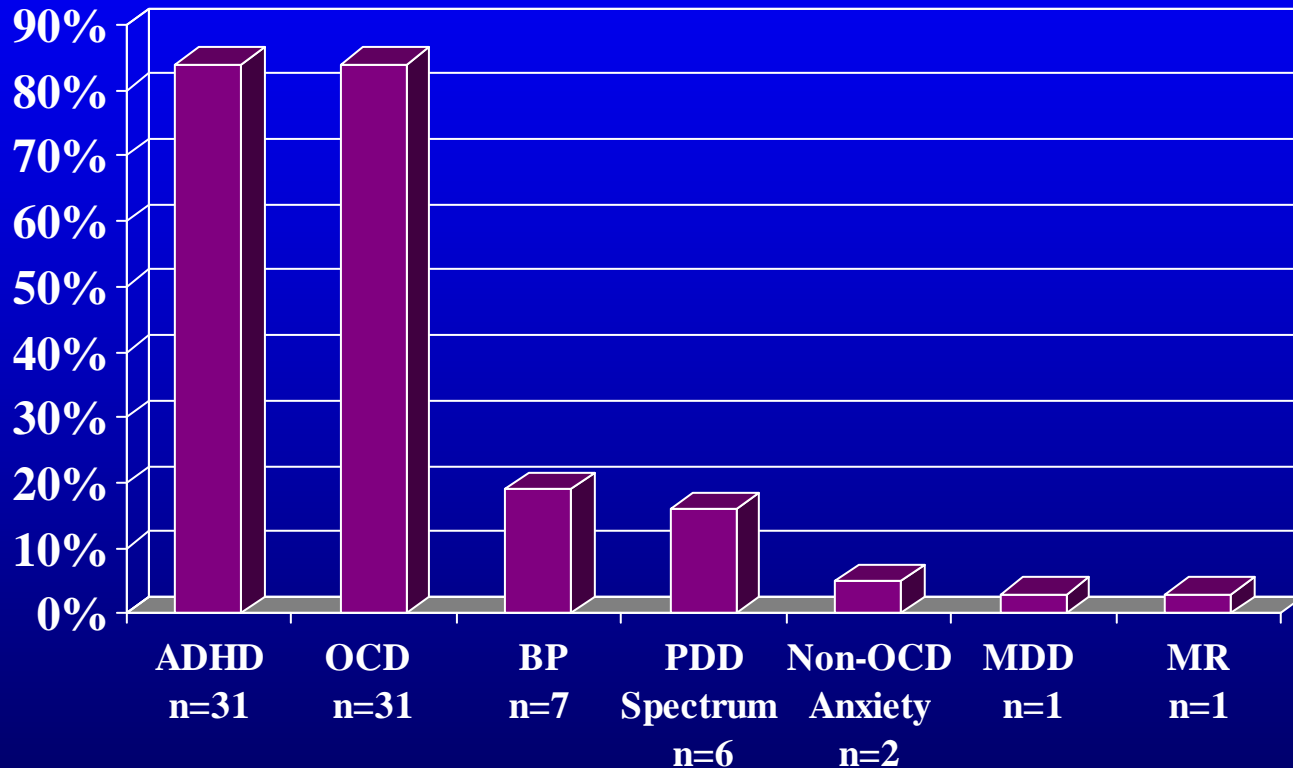
Results: Demographic Features

Mean age:	13.4 years \pm 2.8 (range: 8-18 years)
Comorbid IED:	78%
Sex:	70% male, 30% female
Concurrent meds:	76% \geq 1 psychotropic
Aripiprazole dosage:	11.69 mg daily \pm 7.15 (range 2.5- 40 mg daily)

Current DSM-IV-TR Comorbid Diagnoses

<u>Comorbidity</u>	<u>% (n)</u>
OCD	84% (31)
ADHD	84% (31)
BIP	19% (7)
Non-OCD Anx	5% (2)
MDD	3% (1)
PDD	16% (6)

Results: Co-morbidity Characteristics



78% overall sample also met diagnostic criteria for IED
(minus criterion C)

Tic and Rage Effects

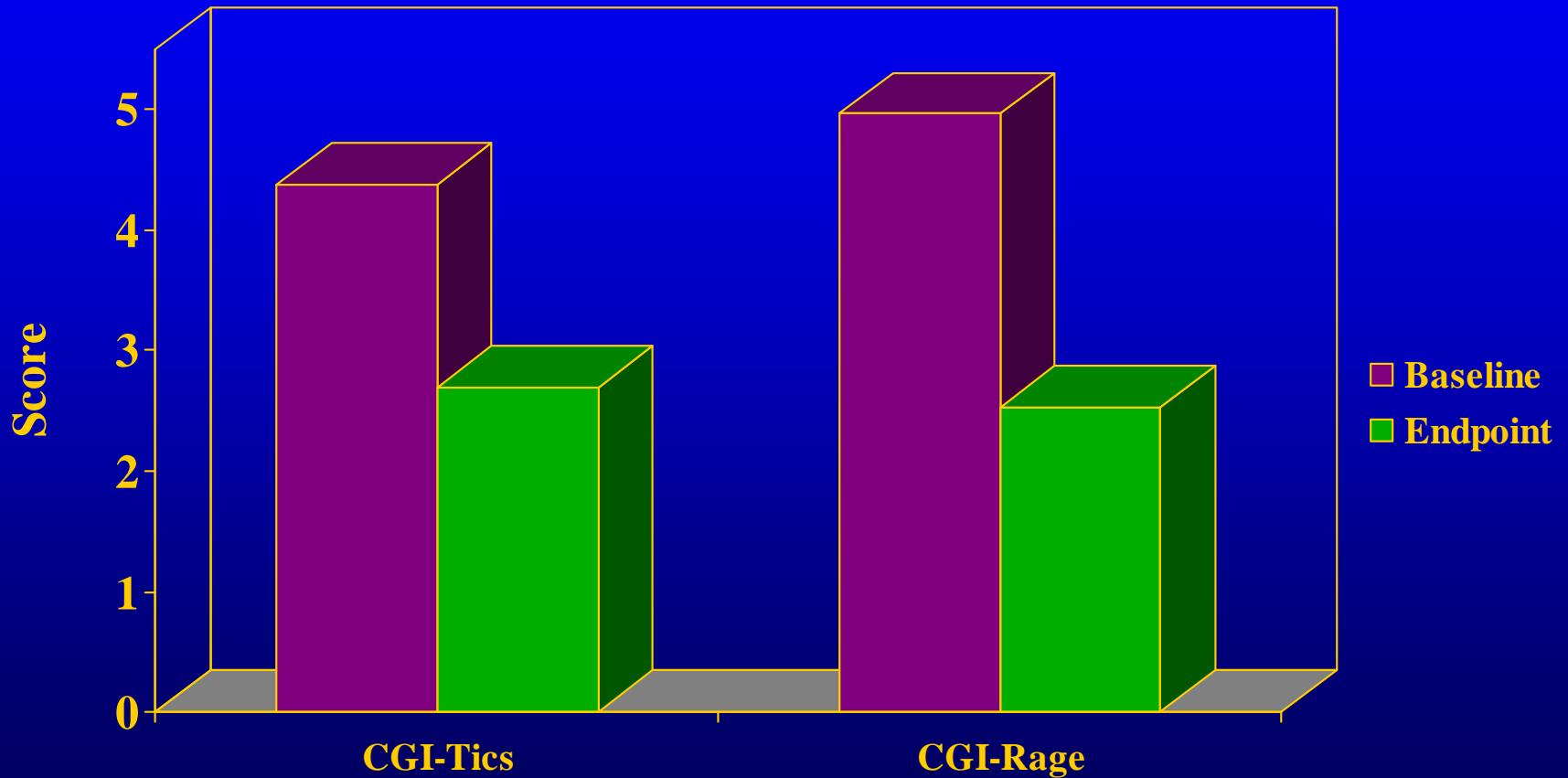
Rating	Baseline	Endpoint
CGI-Tic Mean (SD)	4.38 (0.81)	2.69 (0.88)
CGI-Rage Mean (SD)	4.96 (1.22)	2.53 (1.13)

CGI-Tic: Clinical Global Impression Scale for Tics (n=37)

CGI-Rage: Clinical Global Impression Scale for Rage (n=32)

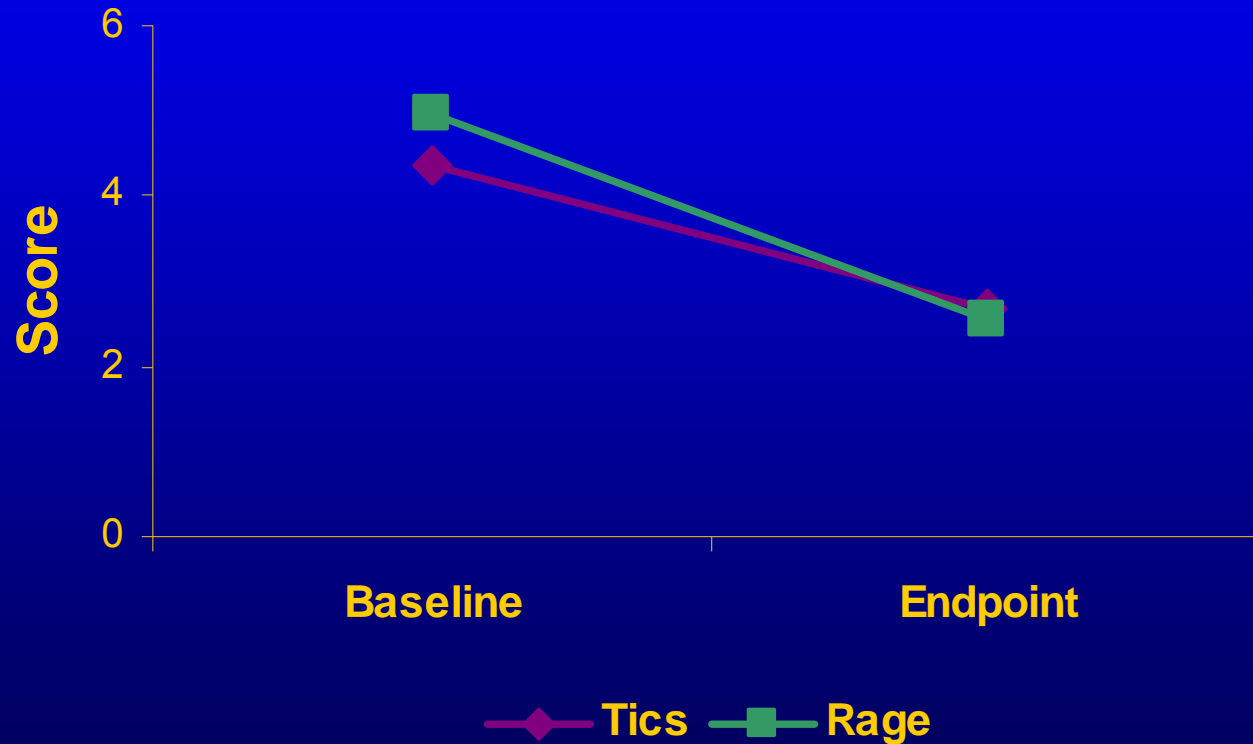
Change in Severity by ≥ 1 point CGI = 100% for tics, 96% for rage

Results: Symptom Reduction



Scores based on the Clinical Global Impression Scales (CGI)

Results: Symptom Reduction



Results: Reasons for Discontinuation

- 8 /37 subjects (22%) discontinued aripiprazole before 12 weeks (including 6 adolescents and 2 pre-pubertal children)
 - 6/37 (16%) akathisia
 - 1/37 (3%) parkinsonism
 - 3/37 (8%) increased agitation
 - 3/37 (8%) excessive affective lability
 - 1/37 (3%) extreme day-time sedation

Mild, transient side effects such as headache, dizziness, nausea and/or sedation were reported by some subjects who elected to continue treatment

Results: Subject Comparison

	78% Completed Study (29/37)	22% Discontinued < 12 wks (8/37)
Age	13.34 years \pm 2.87	13.75 years \pm 1.98
Gender	65.5% male (19/29)	87.5% male (7/8)
Dose	12.33 mg \pm 7.5 (range 5mg - 40mg)	9.38 mg \pm 5.12 (range 2.5mg – 20mg)
OCD	79.3% (23/29)	87.5% (7/8)
ADHD	89.7% (26/29)	62.5% (5/8)
Bipolar	17.2% (5/29)	12.5% (1/8)
SAD	0	12.5% (1/8)

Results

- 15/37 (40%) of sample had documented pre- and post- treatment weights

87% (13/15) had documented weight gain during study period; mean weight gain= 18 lbs \pm 12.3

13%(2/15) showed documented weight loss during 12-week study period

Summary

- Preliminary evidence suggests aripiprazole reduces both tics and explosive outbursts at low-moderate doses in children with TS who had failed to respond and/or were unable to tolerate previous treatments
- 22% discontinued treatment due to emergence of intolerable adverse effects, mostly extrapyramidal symptoms and increased agitation
- Among 15 subjects with data, significant weight gain was an unexpectedly common problem

Treatment of Rage Symptoms in TS

- Psycho-education
- Parent Skills Training
- Family Therapy/Marital Therapy
- Social Skills Training
- Collaborative Problem Solving Strategies
- Anger Management programs
- Dialectical behavioral therapy
- Relapse prevention therapy
- Physical exercise, nutrition, sleep hygiene

(Scahill et al. 2006; Green et al. 2003)

Future Directions

- TS is a well-defined diagnostic group for inclusion in studies of IA in children
- Need additional valid & reliable measures of IA in TS
- Need prospective data on natural history of aggressive symptoms in TS
- Need multimodal treatment clinical trials in TS that study and target aggressive symptoms