

# 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**

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# Background

## Aripiprazole:

possible “dopamine-serotonin system stabilizer”

- partial agonist D2 and 5HT1A,
- antagonist 5HT2A
- mild antagonist activities D3, D4, 5HT7,  $\alpha$ -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)

- $\geq 3$  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

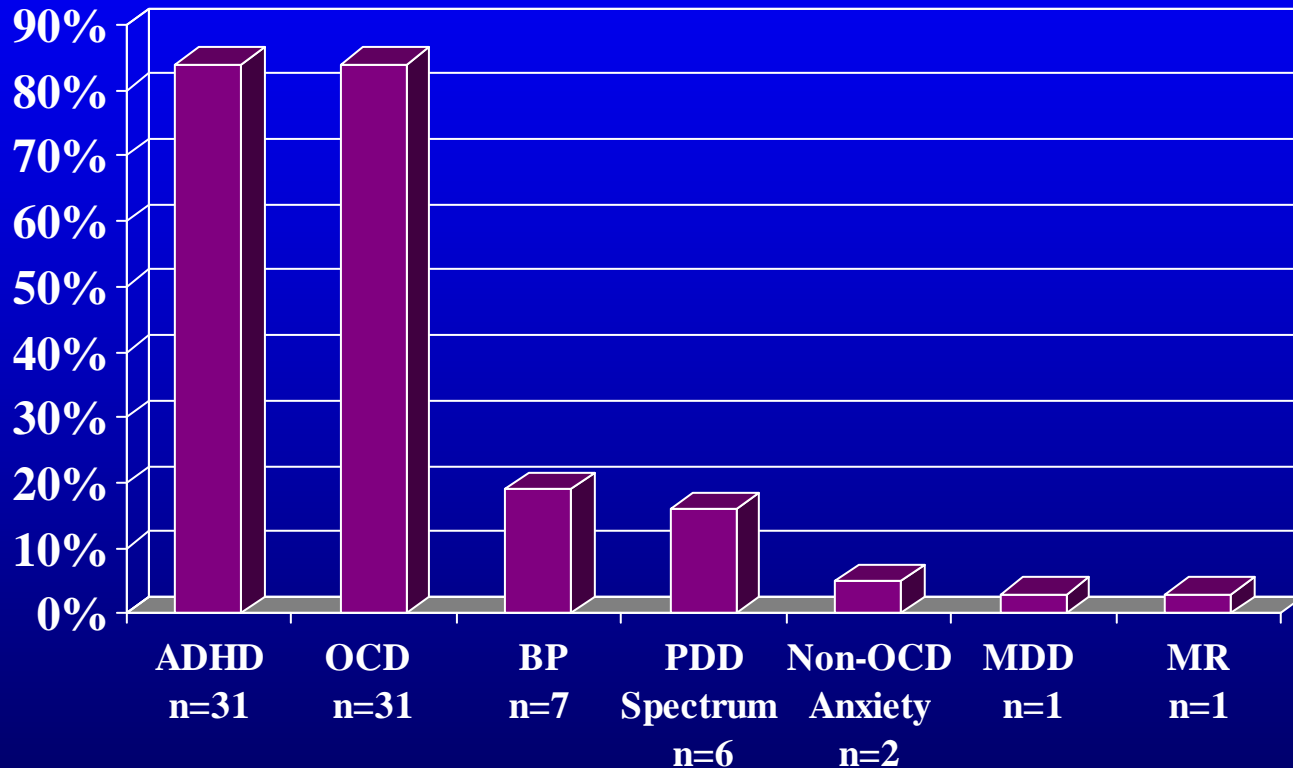
# Results: Demographic Features

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

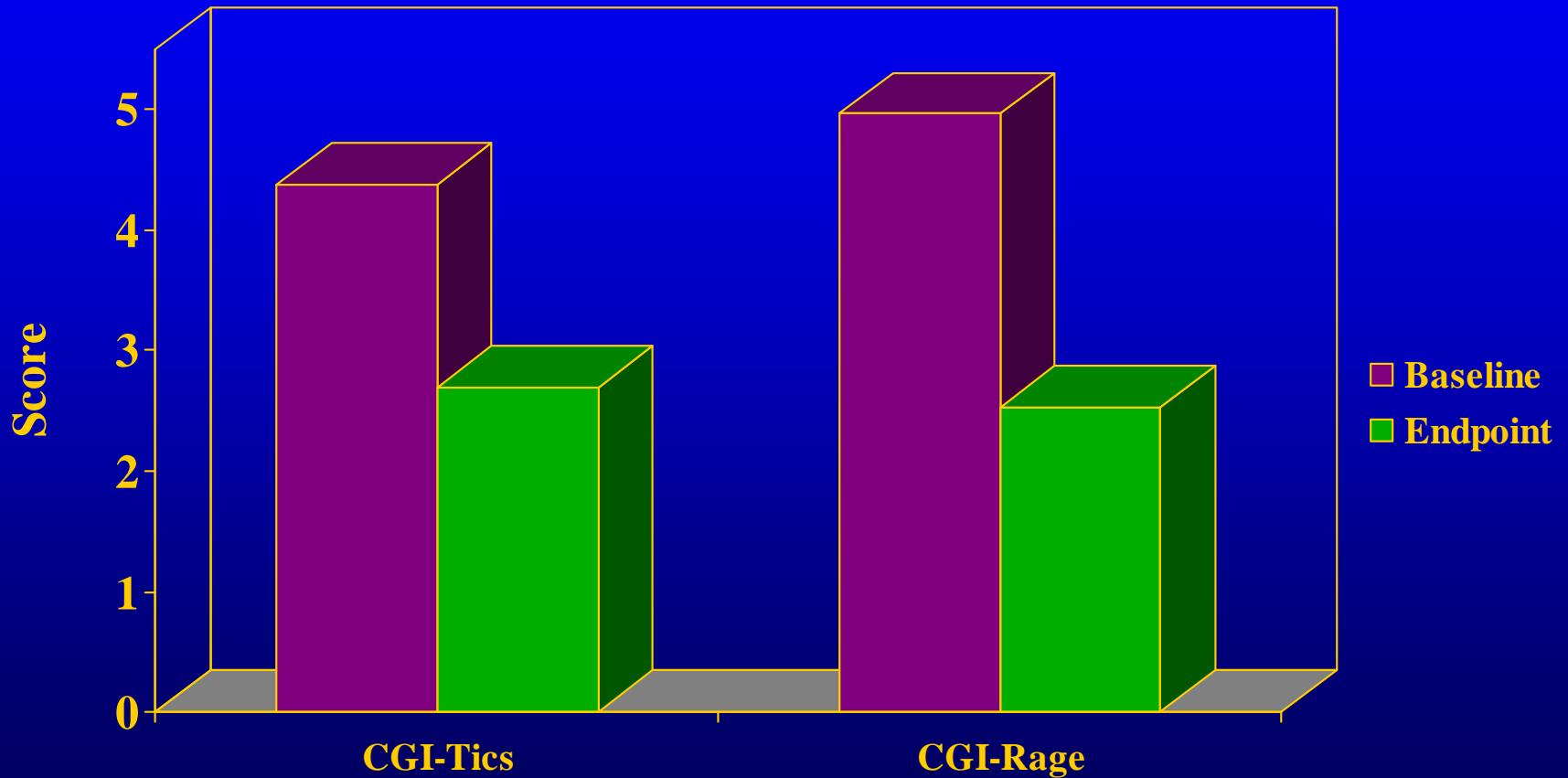
Rating	Baseline	Endpoint
CGI-Tic Mean (SD)	4.38 (0.81)	2.69 (0.88)
CGI-Rage Mean (SD)	4.96 (1.22)	2.53 (1.13)

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

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

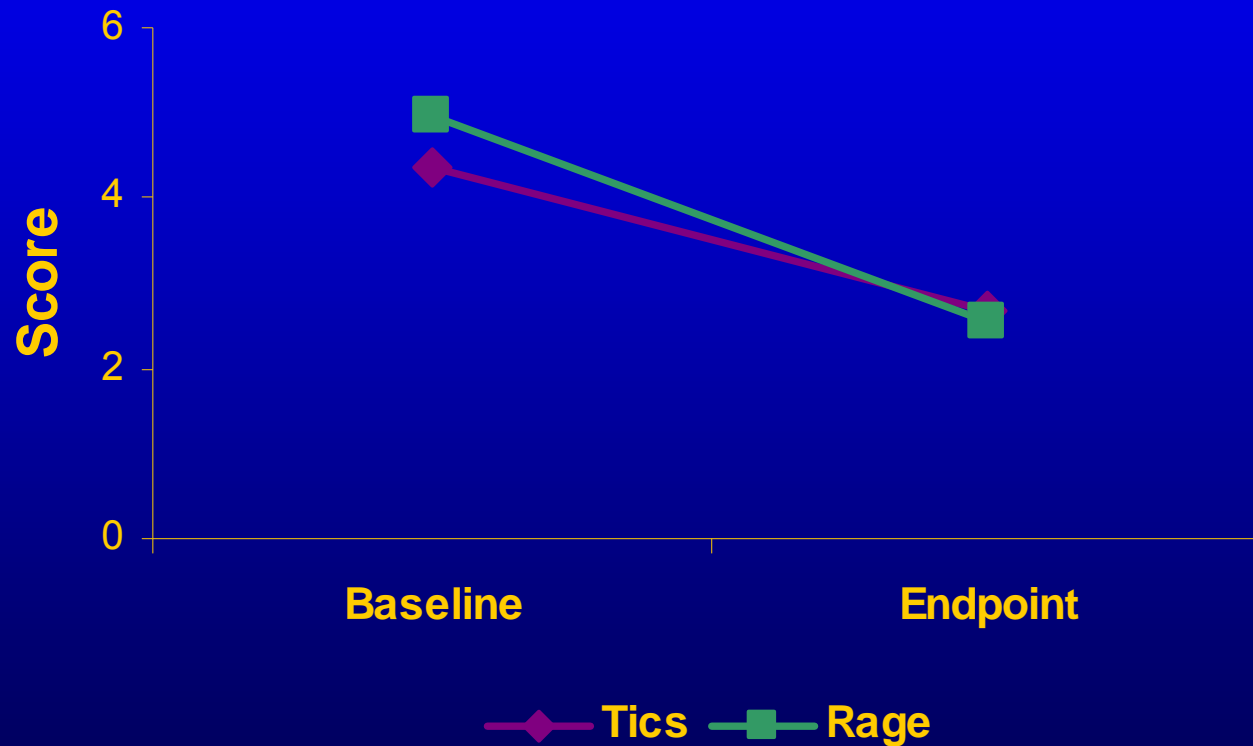
Change in Severity by  $\geq 1$  point CGI = 100% for tics, 96% for rage

# 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