Neuroscience Education Institute

# ASSESSMENT AND TREATMENT OF PEDIATRIC IMPULSIVE AGGRESSION: A TRANSDIAGNOSTIC ISSUE

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# Learning Objectives

- Explain the difference between impulsive and instrumental aggression
- Identify which psychiatric disorders are frequently associated with impulsive aggression
- Recognize when medication might be an important aspect of treating aggression in the context of an Axis I disorder

# How to Recognize the Moods of an Adolescent

HAPPY

DEPRESSED

EXCITED

ANXIOUS

ELATED

AGGRESSIVE

# Overview

- Definitions of aggression
- Identify ways to conceptualize, quantify, and rate levels of aggression
- DSM-5 diagnoses that are commonly associated with aggression
- Psychopharmacology
- Psychotherapy
- Takeaway points

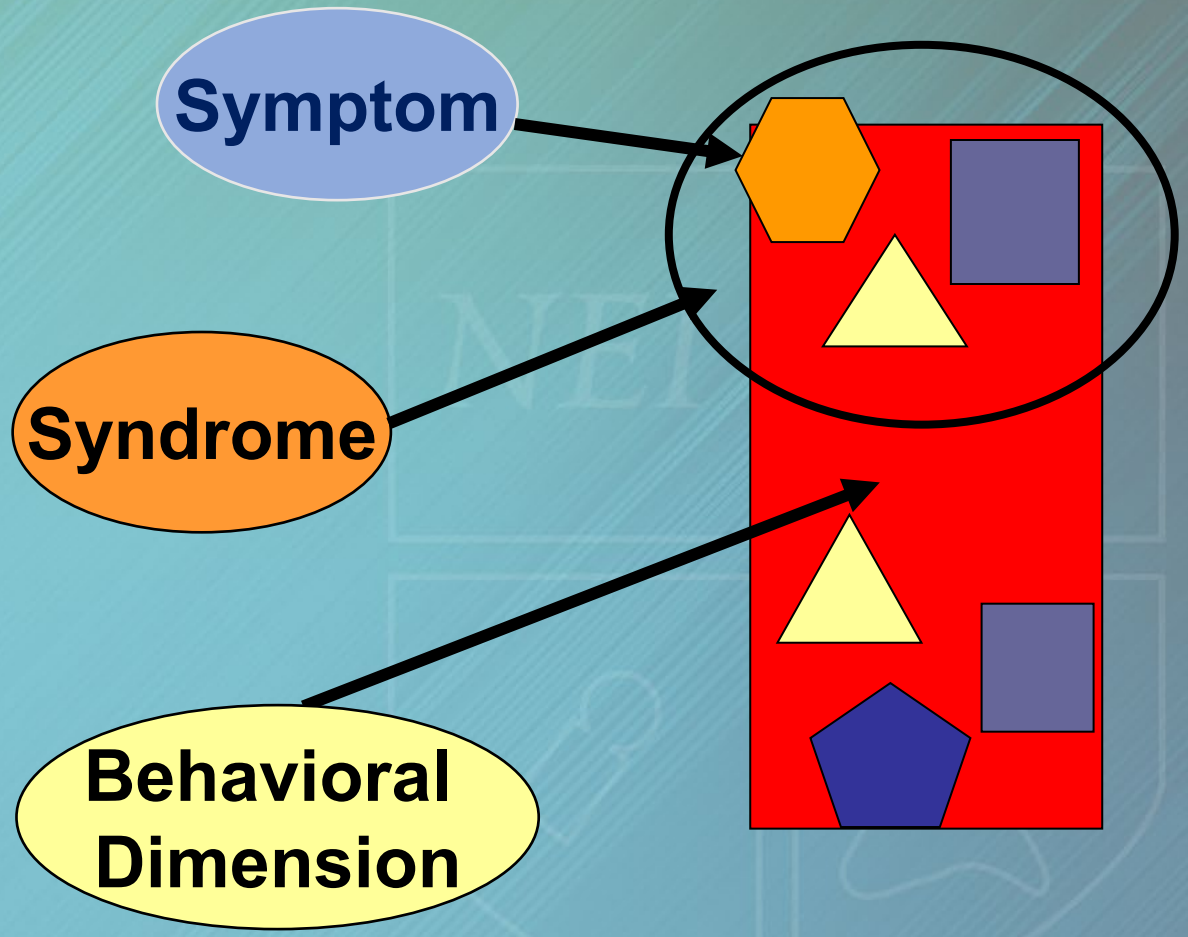
# Definition Impulsive v Instrumental Aggression

- **Emotional or impulsive aggression** refers to *aggression that occurs with only a small amount of forethought or intent and that is determined primarily by impulsive emotions*.
  - Emotional aggression is the result of the extreme negative emotions we're experiencing at the time that we aggress and is not really intended to create any positive outcomes.
- **Instrumental or cognitive aggression**, on the other hand, is *aggression that is intentional and planned*.
  - Instrumental aggression is more cognitive than affective and may be completely cold and calculating. Instrumental aggression is aimed at hurting someone to gain something—attention, monetary reward, or political power, for instance.

# Conceptualize, Quantify, and Rate

# Conceptualize Aggression

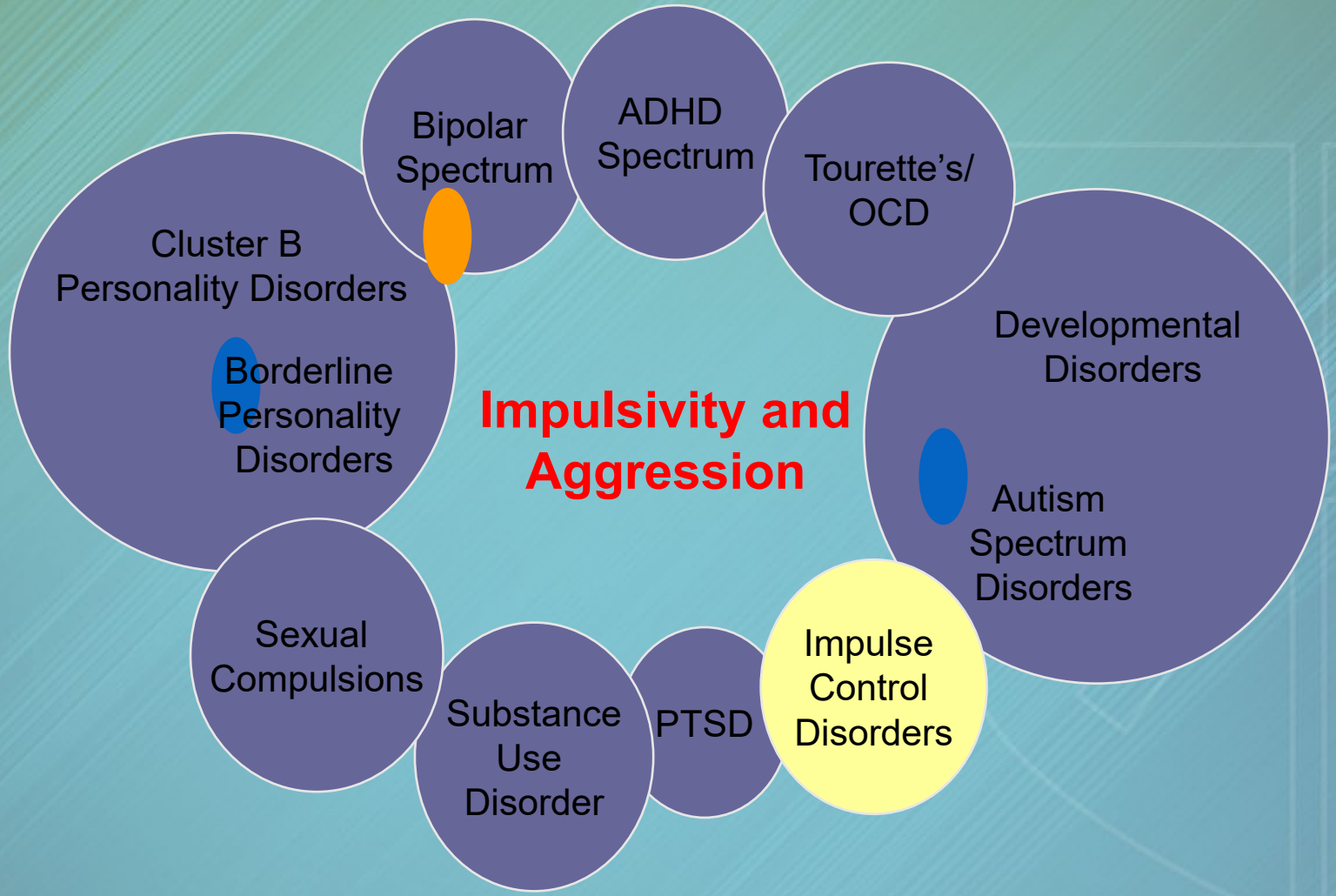
- Symptom
  - Discrete complaint: anxiety, fever, cough
- Syndrome
  - Collection of symptoms occurring together
  - Depression, mania, pneumonia
- Behavioral dimension
  - Behavior with physiological basis
  - Arousal, impulsivity



# Impulsivity: A Symptom

- Contributes to major health problems
  - Violence/aggression
  - Suicide
  - Substance abuse
  - Accidents (e.g., motor vehicle)
- Core symptoms of a broad range of disorders
  - ADHD
  - Autism
  - Bipolar and depressive disorder
  - Disruptive mood dysregulation disorder (DMDD)

# Impulsive-Aggressive Spectrum



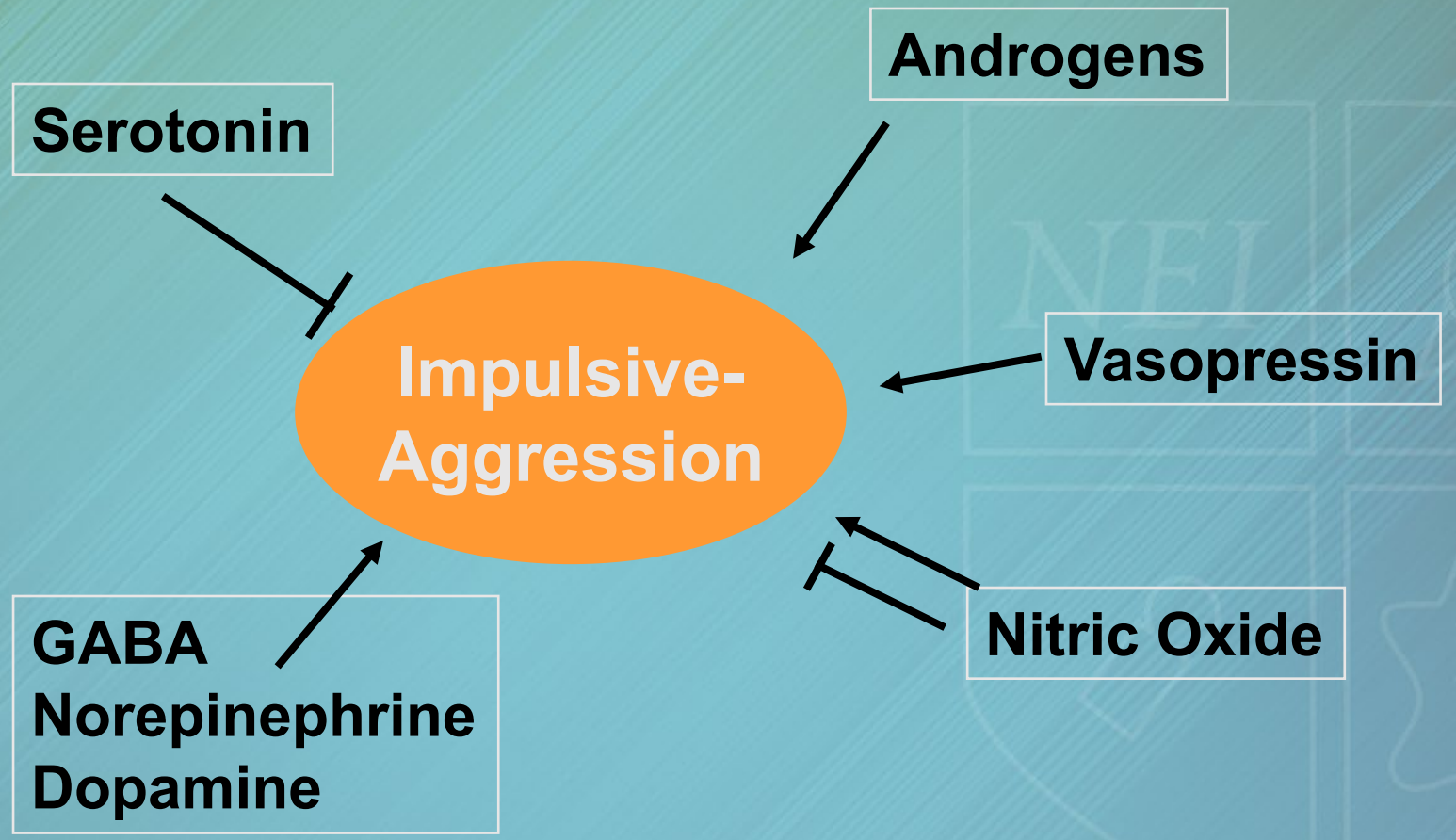
# Rating Scales

- Aggression specific scales
  - Modified overt aggression scale (MOAS) originally done to measure aggression in hospitalized adults; measures verbal and physical aggression including against people and property
- Subscales of a larger scale
  - Irritability subscale of Aberrant Behavior Checklist used in autism for FDA approval of aripiprazole and risperidone for irritability and aggression in autism
- Individual questions in a scale measuring another disorder
  - Mood disorder Young Mania Rating Scale has a question on irritability and aggression, Child Depression Rating Scale has a question on irritability and aggression
- Scales can be used for cutoff, aggressive or not, and to monitor response to treatment

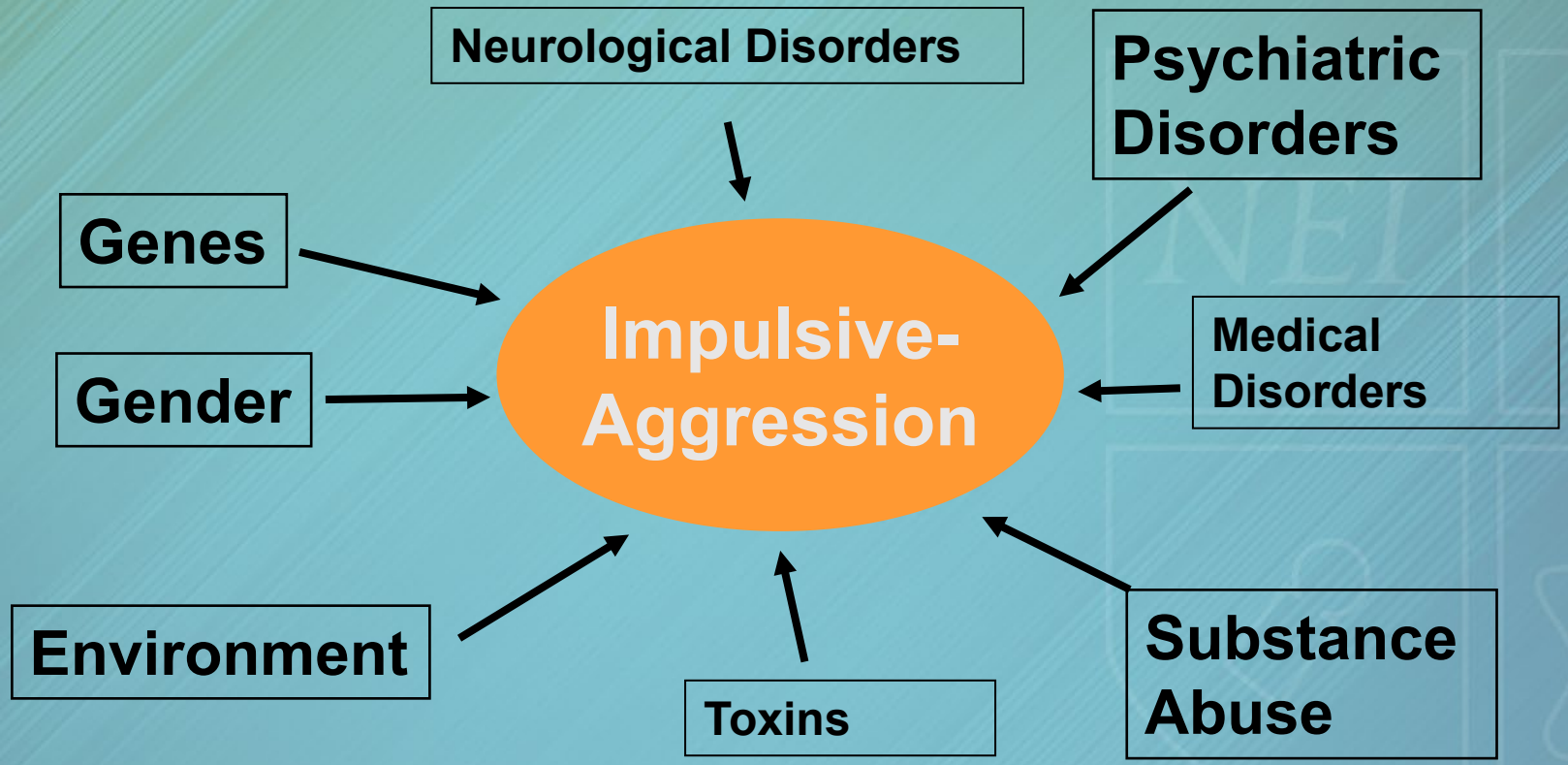
# Aggression Scales—Assessment

- Irritability Scales: Affective Reactivity Index (ARI), Multidimensional Assessment of Pre-school Disruptive Behaviors (MAP-DB)
- Irritability Subscales: Aberrant Behavior Checklist (ABC), Child Behavior Checklist and Youth Self-Report (CBCL/YSR), Young Mania Rating Scale (YMRS)
- Semi-structured interviews:  KSADS
- Aggression Scales: Retrospective-Modified Overt Aggression Scale (R-MOAS)
- Functional Scales: Clinical Global Impression (CGI), Clinical Global Assessment Scale (CGAS)

# Neurochemistry of Impulsive Aggression



# Contributing Factors



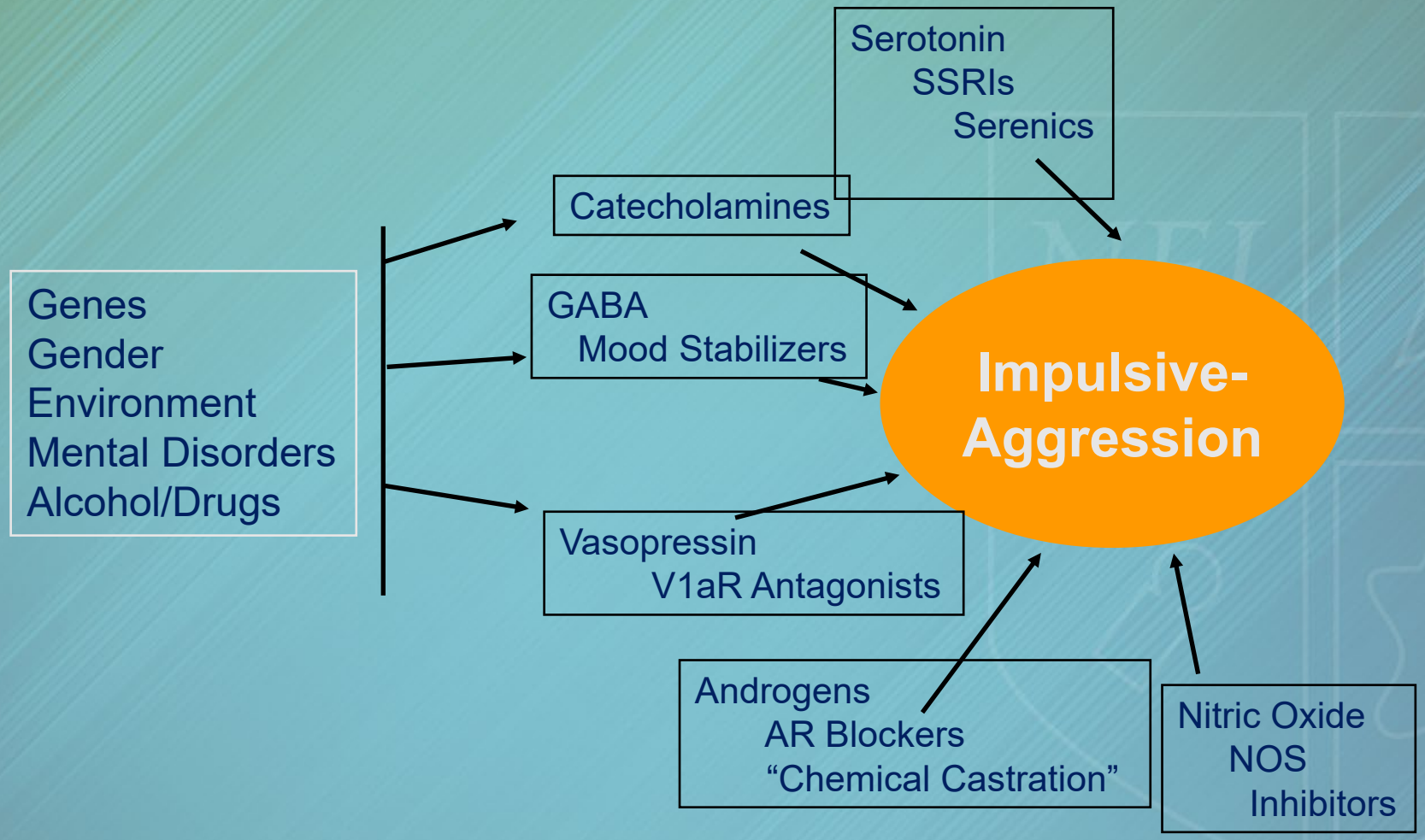
# DSM-5 Disorders

# DSM-5 Disorders

- *ALL* of them can have aggression as a symptom just more or less common in some
- 5 key pediatric psychiatry disorders where aggression is a prominent symptom
  - ADHD
  - DMDD
  - Autism
  - Bipolar and major depressive disorders

# Psychopharmacology: Guiding Principles and Diagnostic Examples

# Lengthening the Fuse: Potential Sites for Intervention



# Anti-Impulsive Medication Classes

- SSRIs
- 5HT1A agonists, 5HT2 antagonists
- Lithium
- Anticonvulsants
- Atypical and typical antipsychotics
- Beta blockers
- Alpha antagonists (e.g., clonidine, guanfacine)
- Opiate antagonists (e.g., naltrexone)
- Dopamine agonists (e.g., stimulants, bupropion)

# *DSM-5* Key Criteria

- **MANIA** 1-week period of elevated, expansive, and/or irritable mood, plus abnormally and persistently elevated goal-directed activity or energy most of the day (if hospitalized or psychotic symptoms mania criteria met even if <1 week)
- **AUTISM** Irritability and aggression are common
- **ADHD** Can have comorbid oppositional or conduct disorder and aggression
- **DMDD** Severe recurrent temper outbursts manifested verbally and/or behaviorally that are grossly out of proportion in intensity or duration to the situation or provocation

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Association; 2013.

# Diagnostic Pointers for DMDD

- Review by Roy notes severe chronic irritability is a non-specific symptom seen in many childhood illnesses
- Developed by team at NIMH to avoid over-diagnosis of bipolar in irritable youth
- Common symptom overlap with ADHD, oppositional defiant disorder, and intermittent explosive disorder
- Very limited data on interventions given the recent description of this diagnosis
- Most data is around treatment of irritability in other disorders

Roy AK et al. Am J Psychiatry 2014;171(9):918-24.

# Psychopharmacology DMDD and ADHD

- Trial of stimulants in 68 youth with ADHD and severe mood dysregulation
- 65 entered medication phase with 64% having stimulant adjusted at study entry (sub-optimal dosing); 3 did not meet DSM-5 criteria for DMDD
- Efficacy for 38 youth with DMDD and stimulant adjustment
- Stimulant optimization resulted in improved depressive symptoms on Child Depression Rating Scale (CDRS) and Mood Deverity Index (MSI), NOT on Young Mania Rating Scale YMRS
- Still had significant impairment at end of 6 weeks

Baweja R et al. J Child Adolesc Psychopharmacol 2016;26(2):154-63.

# Improvements in Irritability With Open-Label Methylphenidate Treatment in Youth With Comorbid ADHD and DMDD

- Open-label study of long-acting methylphenidate (MPH) treatment on irritability and related emotional symptoms associated with disruptive mood dysregulation disorder (DMDD) in youth with comorbid attention-deficit/hyperactivity disorder (ADHD)
- 22 medication-free male and female subjects (ages 9–15) met criteria for both DMDD and ADHD
- 4-week trial of long-acting MPH treatment (Concerta), with weekly dosing increases until therapeutic dose was reached
- Primary outcome was self-report irritability; secondary outcomes included parent and child ratings of emotional frequency, emotional lability, and negative affect (NA)
- Significant improvements (medium to large effect sizes) in child-rated irritability as well as parent and child ratings of emotional lability, NA, and anger were found; ADHD symptoms also improved
- Majority of the sample saw improvement in child-rated irritability (71%), symptoms worsened in a small proportion (19%), and an even smaller portion experienced no change (10%)

Winters DE et al. J Child Adolesc Psychopharmacol 2018;28(5):298-305.

# Irritability With Open-Label Methylphenidate Treatment in Youth With Comorbid ADHD and DMDD

**Primary Outcome**: child-rated improved moderate effect size after treatment with MPH.

**Secondary Outcomes**: measures of parent-rated emotional regulation improved with a large effect size after treatment with MPH. 68% had an improvement in emotional outburst ratings on the ERC.

Measures of ADHD symptoms improved significantly.

TABLE 2. *t*-TEST RESULTS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EMOTIONAL MEASURES ($N=22$)

| | *Pretest* | | *Posttest* | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Variable* | M | *SD* | M | *SD* | *95% CI for mean difference* | d | t | *df* |
| Primary | | | | | | | | |
| Irritability scale | 44.95 | 6.47 | 40.97 | 8.29 | −7.14 to −0.82, | 0.57++ | −2.62* | 20 |
| Secondary | | | | | | | | |
| ERC | | | | | | | | |
| Lability | 41.64 | 6.06 | 34.68 | 6.81 | −30.39 to −23.79 | 0.85+++ | −4.00** | 21 |
| Regulation[a] | 23.09 | 4.15 | 24.45 | 2.53 | −0.72 to −3.44 | 0.29+ | 1.36 | 21 |
| DES–IV | | | | | | | | |
| Anger | 9.95 | 2.57 | 8.70 | 2.83 | −2.83 to −0.07 | 0.55++ | −2.20* | 19 |
| Surprise | 10.00 | 2.23 | 8.30 | 2.52 | −3.33 to −0.17 | 0.49++ | −2.31* | 19 |
| Shame | 10.23 | 2.84 | 8.95 | 2.67 | −2.86 to −0.24 | 0.56++ | −2.46* | 19 |
| Interest | 10.36 | 3.14 | 9.55 | 2.82 | −3.22 to 0.82 | 0.27+ | −1.24 | 19 |
| Joy | 10.45 | 2.70 | 9.75 | 2.88 | −2.18 to 1.28 | 0.12 | −0.54 | 19 |
| Sadness | 9.05 | 2.61 | 12.0 | 7.80 | −3.09 to 0.29 | 0.39+ | −1.73 | 19 |
| Disgust | 8.32 | 2.77 | 15.0 | 7.75 | −1.90 to 0.90 | 0.18 | −0.75 | 19 |
| Contempt | 7.50 | 2.87 | 11.0 | 6.80 | −2.01 to 0.91 | 0.18 | −0.79 | 19 |
| Hostility | 7.27 | 2.75 | 14.0 | 6.70 | −2.29 to 0.89 | 0.21+ | −0.92 | 19 |
| Fear | 1.18 | 3.16 | 13.0 | 6.85 | −2.63 to 1.23 | 0.17 | −0.76 | 19 |
| Shyness | 8.36 | 3.11 | 12.0 | 7.50 | −2.85 to 0.65 | 0.30+ | −1.32 | 19 |
| Guilt | 9.0 | 2.51 | 12.0 | 8.50 | −1.70 to 0.51 | 0.25+ | −1.13 | 19 |
| PANAS-C | | | | | | | | |
| Negative affect | 37.55 | 9.90 | 32.36 | 12.27 | −8.18 to −0.14 | 0.50++ | −2.17* | 18 |
| Positive affect[a] | 44.18 | 9.26 | 42.11 | 8.61 | −7.11 to 2.48 | 0.23+ | −1.01 | 18 |
| ADHD | | | | | | | | |
| Hyperactivity | 17.09 | 6.04 | 10.36 | 7.35 | −10.09 to −3.36 | 0.89+++ | −4.16** | 21 |
| Inattention | 22.77 | 4.18 | 12.0 | 5.94 | −14.12 to −7.43 | 1.43+++ | −6.71** | 21 |
| Raw score | 39.86 | 8.21 | 22.36 | 12.63 | −23.67 to −11.33 | 1.26+++ | −5.91** | 21 |

[a]Reverse scored.
*$p<0.05$, **$p<0.001$ two-tailed significance.
Effect size: +, small (0.20); ++, medium (0.50); +++ large (0.80).
ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; *d*, Cohen's *d*; DES-IV, Differential Emotions Scale-IV; df, degrees of freedom; ERC, Emotion Regulation Checklist; *M*, mean; PANAS-C, Positive and Negative Affectivity Scale for Children; SD, standard deviation; *t*, t-statistic.

Winters DE et al. J Child Adolesc Psychopharmacol 2018;28(5):298-305.

# A Double-Blind Randomized Placebo-Controlled Trial of Citalopram Adjunctive to Stimulant Medication in Youth With Chronic Severe Irritability

- Trial of the effects of adding citalopram (CTP) versus placebo (PBO) to methylphenidate (MPH) in the treatment of chronic severe irritability in youth using a double-blind randomized placebo-controlled design
- Lead-in phase of open treatment with stimulant in 69 youth; 53 youth meeting criteria for severe mood dysregulation (SMD) were randomly assigned to receive CTP (25) or PBO (28) for 8 weeks
- Titrated q5 days from 5 to 20 mg up to max dose 40 mg mean 29.3 mg (1 wd at 4 days excluded)
- Master clinicians did CGI-I CGI-S PARS, CDRS
- Categorical outcome CGI-I 1 or 2 is improved as responder

Towbin K et al. J Am Acad Child Adolesc Psychiatry 2020;59(3):350-61.

# A Double-Blind Randomized Placebo-Controlled Trial of Citalopram Adjunctive to Stimulant Medication in Youth With Chronic Severe Irritability

- 49 participants—48 of them (98%) meeting disruptive mood dysregulation disorder (DMDD) criteria—were included in the intent-to-treat analysis
- Primary outcome measure was the proportion of response based on improvements of irritability at the 8th week of the trial
- Secondary outcome was changes in CGAS, PARS, and CDRS
- First 4 participants, 2 each group, excluded due to technical difficulties
- 49 in intent-to-treat (ITT) analysis and 41 completed; 1 needed week 7 due to elevate AST and ALT >3X ULN stopped with cessation of methylphenidate

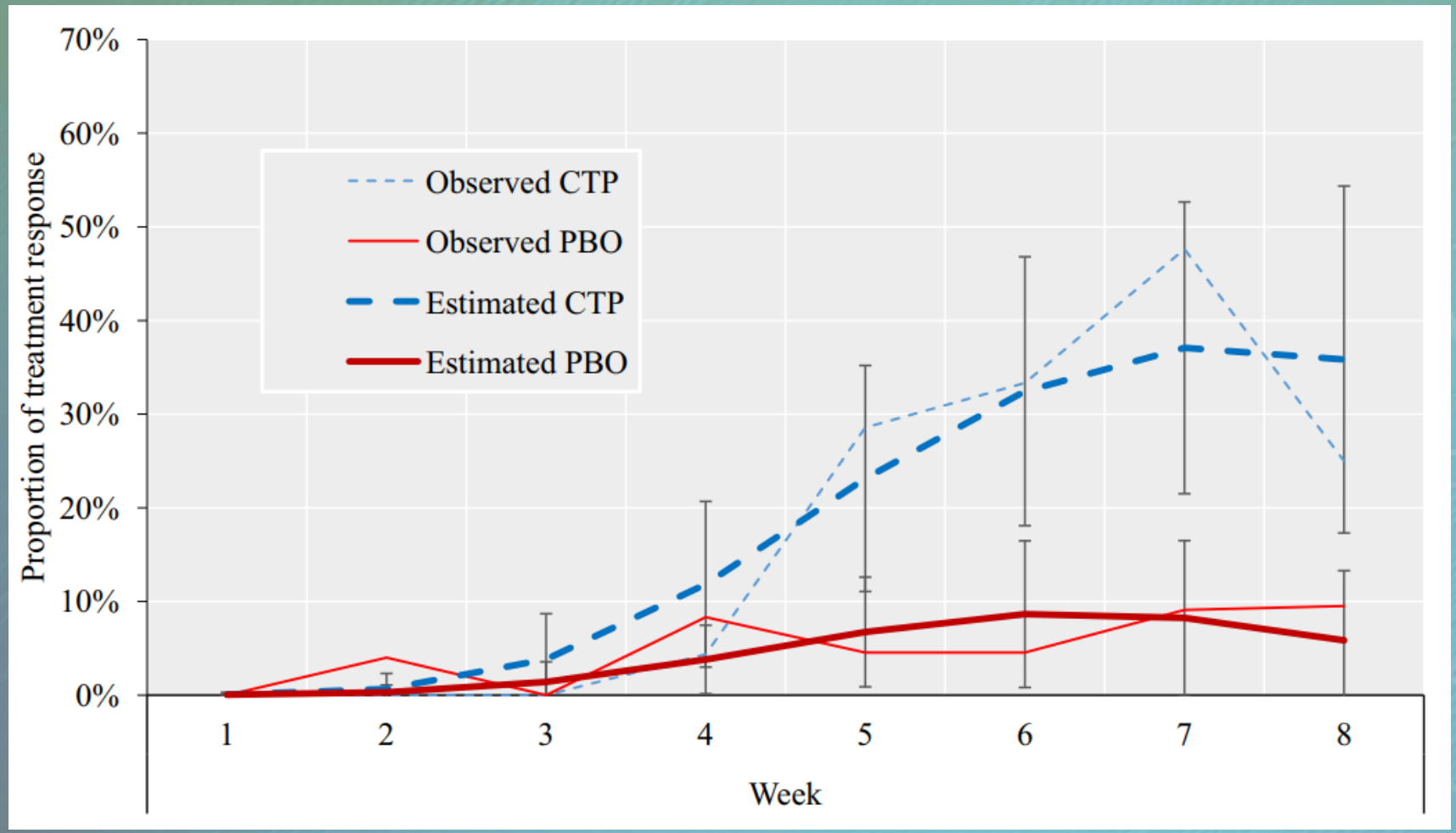
Towbin K et al. J Am Acad Child Adolesc Psychiatry 2020;59(3):350-61.

# Results Open and Closed Trial

- Open-label stimulant optimization, 11 people well enough to dc before randomization
- Benefits of stimulant include decrease in hyperarousal ES 1.10 temper outbursts 0.54, no effect on mood outbursts
- Blinded results of CTP or PBO CTP+MPH compared to PBO+MPH (35% CTP+MPH vs. 6% PBO+MPH; OR=11.70, 95%CI 2.00, 68.16, p=0.006)
- No differences in functional impairment between groups at the end of the trial
- No differences were found in any adverse effect between treatment groups
- No hypomanic or manic symptoms
- Adjunctive CTP might be efficacious in the treatment of chronic severe irritability in youth resistant to stimulant treatment alone

Towbin K et al. J Am Acad Child Adolesc Psychiatry 2020;59(3):350-61.

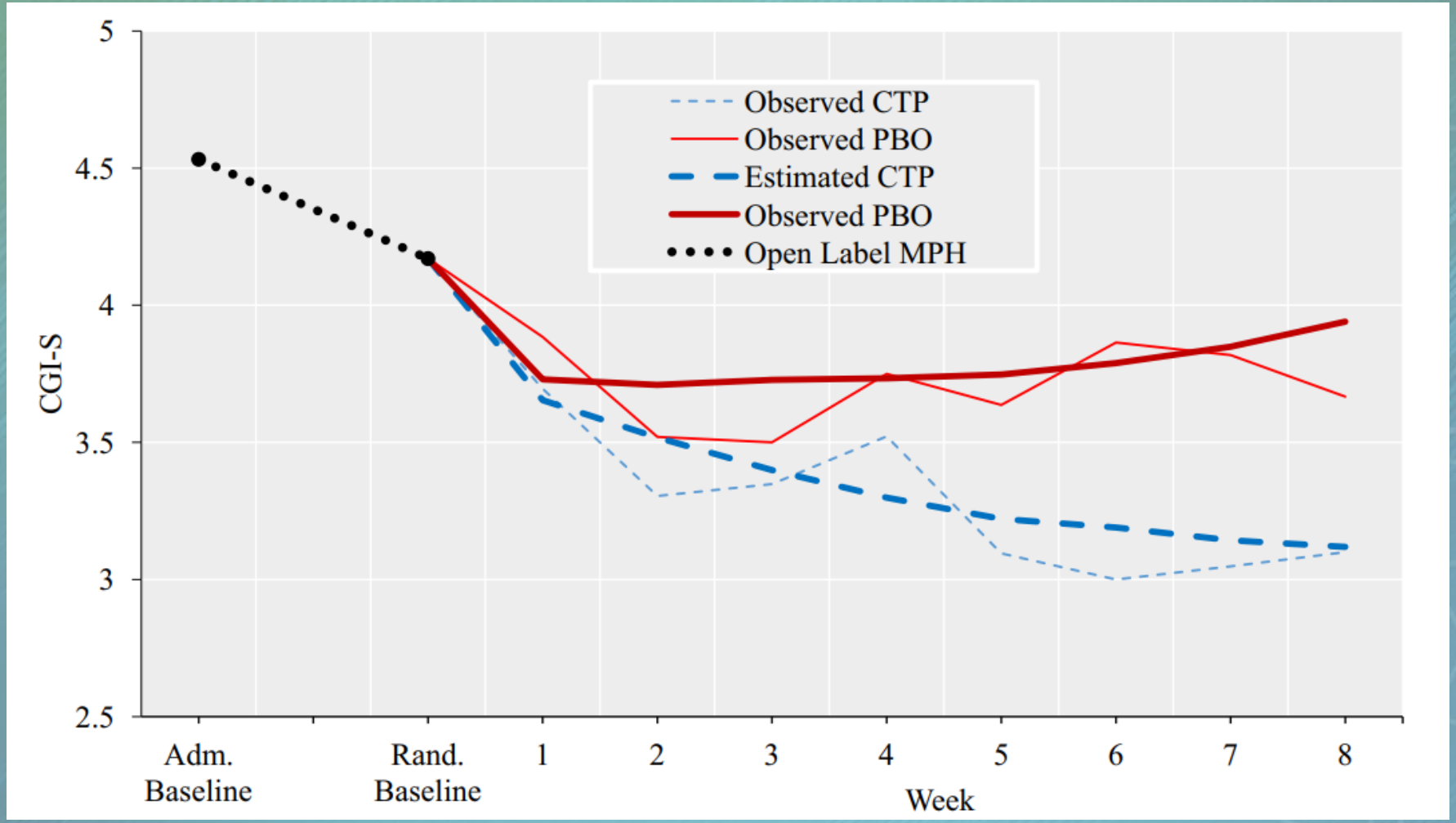
# Proportion of Treatment Response by Week and Treatment Group




CTP citalopram
PBO placebo
NNT 3 better by drug

Towbin K et al. J Am Acad Child Adolesc Psychiatry 2020;59(3):350-61.

# Change in Irritability Severity Before and After Randomization in ITT Analysis




Towbin K et al. J Am Acad Child Adolesc Psychiatry 2020;59(3):350-61.

# Effective Use of Atomoxetine to Treat Six Inpatient Youths With DMDD Without Attention Deficit Disorder

- Atomoxetine second line for ADHD as presynaptic norepinephrine transporter, more useful in those with anxiety and depression
- Two meta-analyses of RCTs in adults show positive impact on emotional lability in addition to ADHD symptoms
- Children and adolescents' anecdotal reports positive impact of atomoxetine (ATX) in patients with neurodevelopmental disorder associated with cognitive difficulties such as sluggish cognitive tempo, dyslexia, and PDD
- Used ATX in six resistant cases with severe chronic irritability and matching DMDD
- Five showed a dramatic clinical improvement
- Chart review of psychiatric inpatients at two tertiary care hospitals 10/16–10/18
- Overlap in diagnosis between ADHD and DMDD (50–80%)
- Only youth who have DMDD **without** ADHD were included to eliminate improvement of ADHD symptoms as cause of all improvement

Benarous X et al. CNS Spectr 2020;25:455-7.

# Effective Use of Atomoxetine to Treat Six Inpatient Youths With DMDD Without Attention Deficit Disorder

- Outcomes based on Clinical Global Impression-Improvement (CGI-I)
- Differences in Affective Reactivity Index (ARI) score
- Buss-Durkee Hostility Inventory score (BDHI)
- Child Global Assessment of Functioning from admission to discharge
- Number of weekly physical restraints
- Changes in weekly PRN medications
- Use week prior to ATX as baseline and changes at week 2, 3, 4 after steady state of maximum ATX
- Age 10–14, 4 male, 2 female, all with comorbid anxiety diagnosis

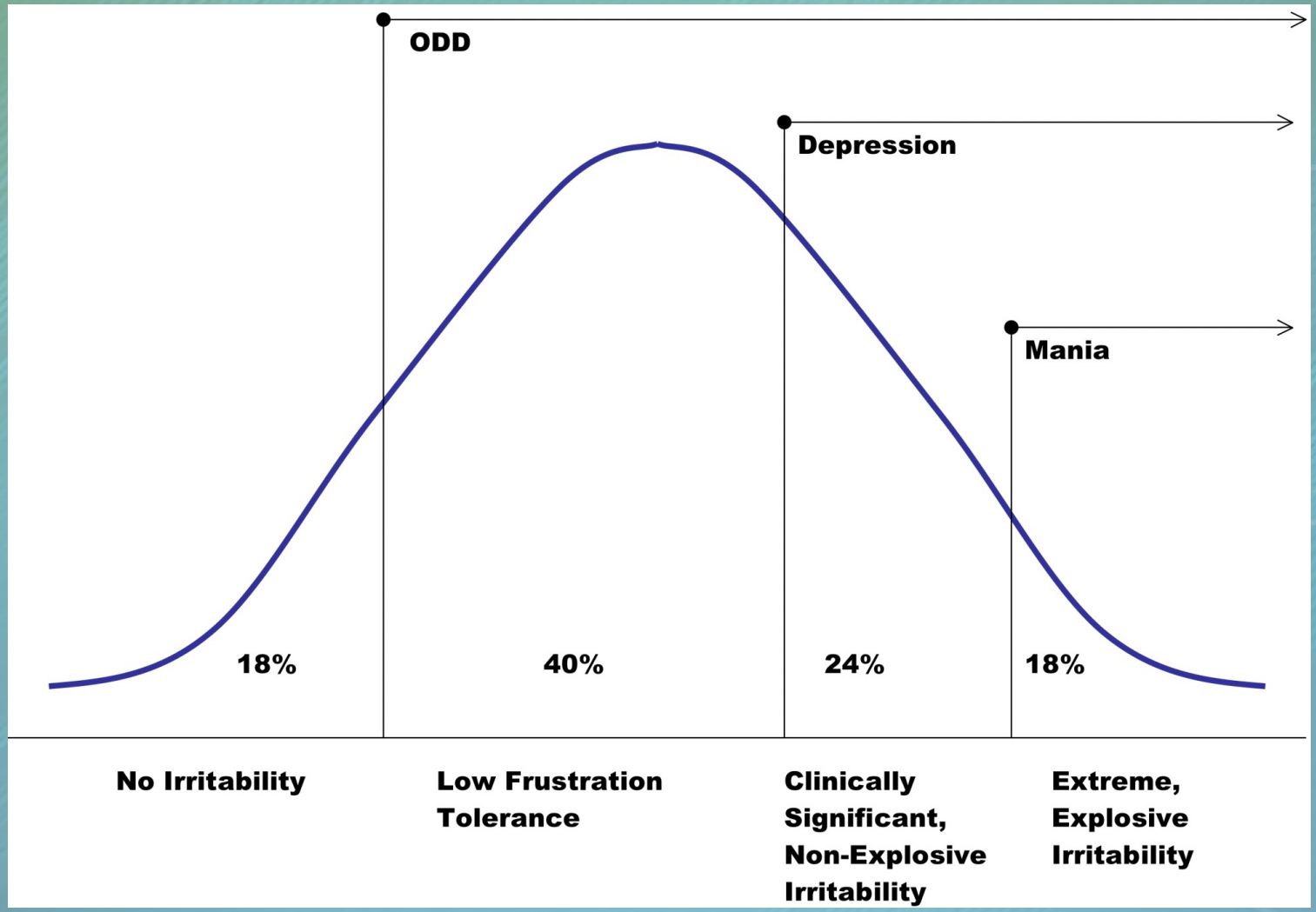
Benarous X et al. CNS Spectr 2020;25:455-7.

# Effective Use of Atomoxetine to Treat Six Inpatient Youths With DMDD Without Attention Deficit Disorder

- Mean ATX starting dose: 20 mg/d (0.46 mg/kg/d)
- Mean ATX discharge dosage: 63 mg/d (1.20 mg/kg/d)
- Number of weeks to achieve maximum dose: 3–5
- C-GAF scores: average change value +50.8
- CGI-I: 5 patients very much improved, 1 patient minimally improved
- ARI scores at entrance: 24 (+/- 2.53)
- ARI scores at discharge: 6.68 (+/- 6.49) 73% reduction, $p<.001$
- BDHI scores at entrance: 102.2 (+/- 13.6)
- BDHI scores at discharge: 54.5 (+/- 19.5) 46% decrease, $p<.001$
- Number of restraints dropped from 7.67 to 4.17 after 2 weeks
- Frequency of prn medications dropped from 4.83 to 3.67
- No readmission within 60 days of discharge

Benarous X et al. CNS Spectr 2020;25:455-7.

# Irritable Mood in Children and ADHD




Mick E et al. Biol Psychiatry 2005;58(7):576-82.

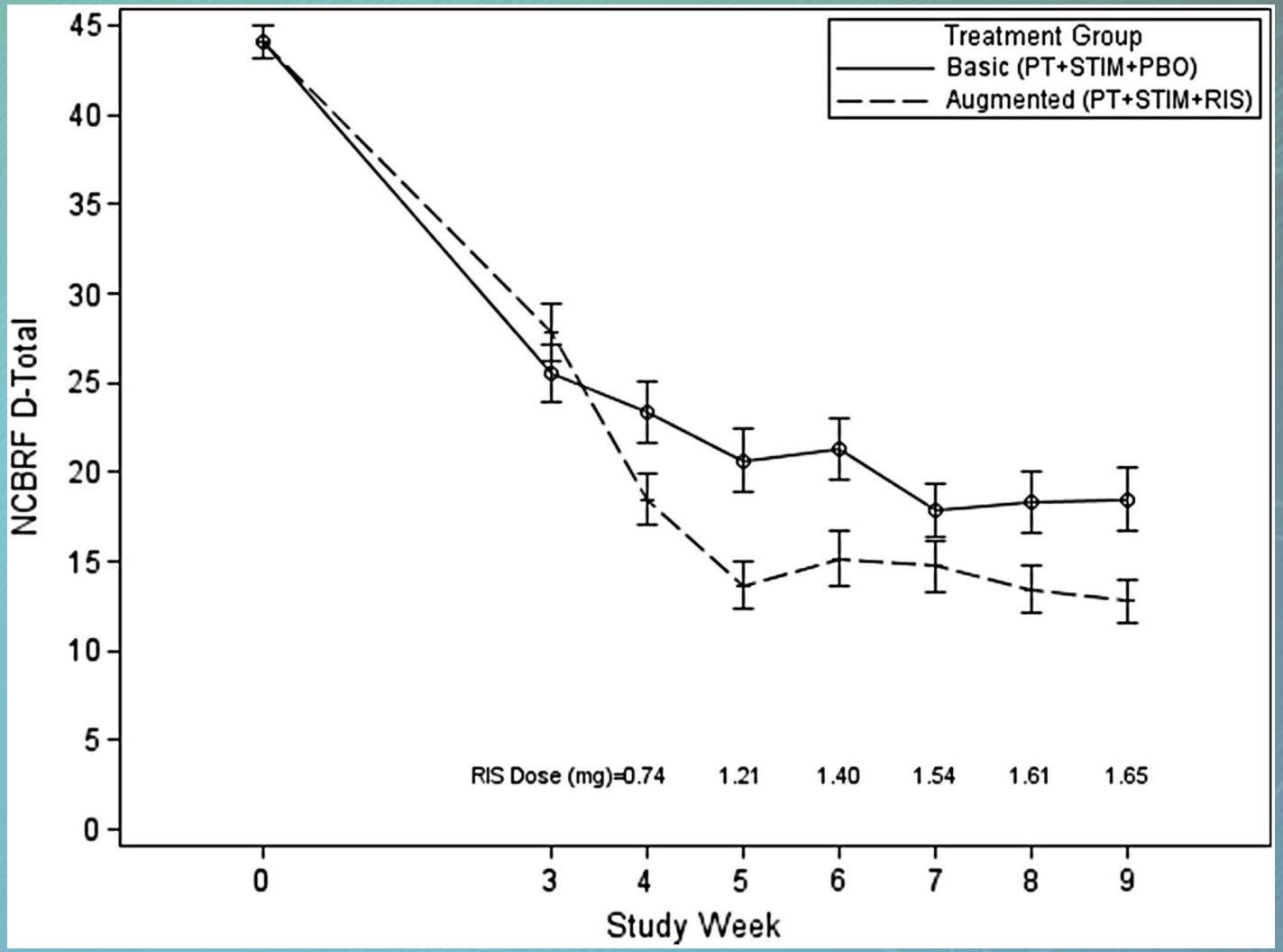
# What Does Risperidone Add to Parent Training and Stimulants for Severe Aggression in Child ADHD?

- 4-site RCT
- ADHD plus severe physical aggression (ODD N=124; CD N=84)
- 9-week trial comparing PT + STIM + placebo (basic treatment; n=84) with PT + STIM + RIS (augmented treatment; n=84)
- Children received psychostimulant (usually OROS methylphenidate) for 3 weeks, titrated for optimal effect, while parents received PT
- If there was room for improvement at end of week 3, placebo or risperidone was added
- Assessments included parent ratings on the Nisonger Child Behavior Rating Form (Disruptive-Total subscale was the primary outcome) and Antisocial Behavior Scale; blinded clinicians rated change on the Clinical Global Impressions Scale

Aman MG et al. J Am Acad Child Adolesc Psychiatry 2014;53(1):47-60.e1.

# Risperidone Improved Outcome in Stimulant Treated Aggressive Children With ADHD

Treatment-by-time interaction, p=0.0049




Aman MG et al. J Am Acad Child Adolesc Psychiatry 2014;53(1):47-60.e1.

# Aggression and Severe Disruptive Behavior in Autism

- Irritability and agitation
- Self-injurious behaviors (SIB)
- Property destruction
- Outbursts of frustration and distress
- “Tantrums/meltdowns”

# Pharmacotherapy for Irritability and Disruptive Behavior

- Atypical (second-generation) antipsychotics (aripiprazole, risperidone)
  - Strong evidence for risperidone and aripiprazole in reducing irritability, self-injury, and hyperactivity
  - **First-line treatment**
  - **FDA-approved to treat irritability in ASD-already approved**
- α2 adrenergic agonists (clonidine, guanfacine)
  - Small studies demonstrating beneficial impact on hyperactivity (e.g., Jaselskis et al. 1992), but limited evidence on irritability and SIB

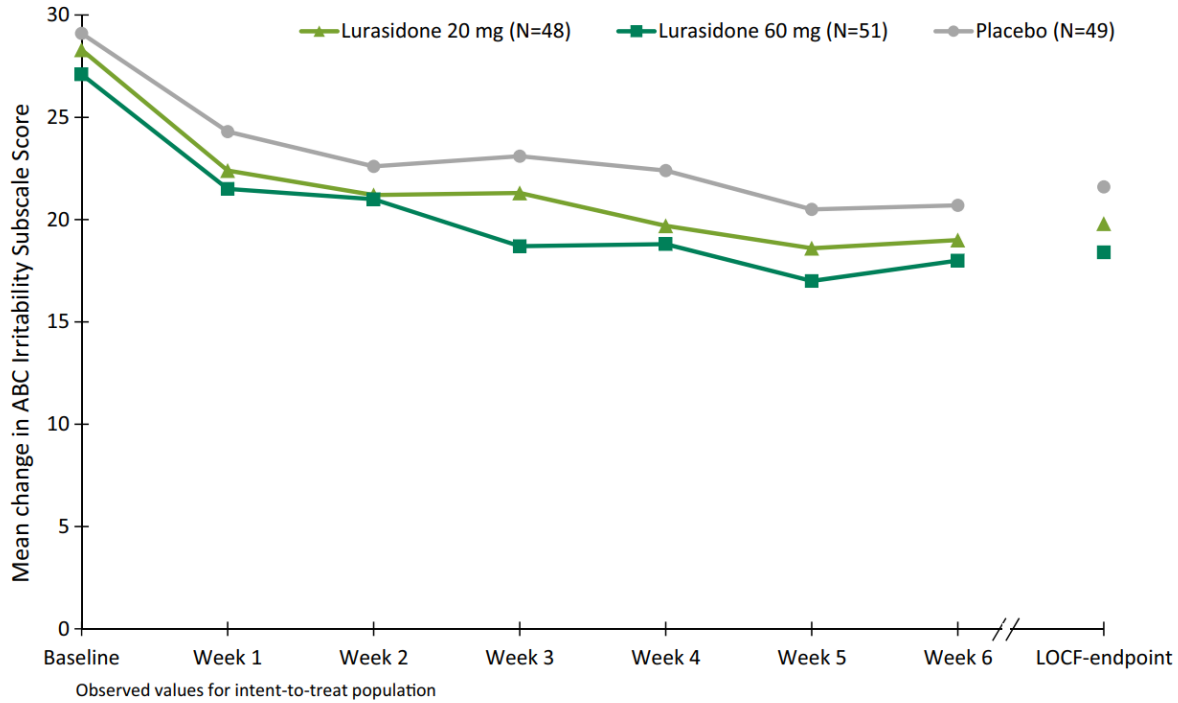
Hyman SL et al. Pediatrics. 2020;145(1):e20193447.

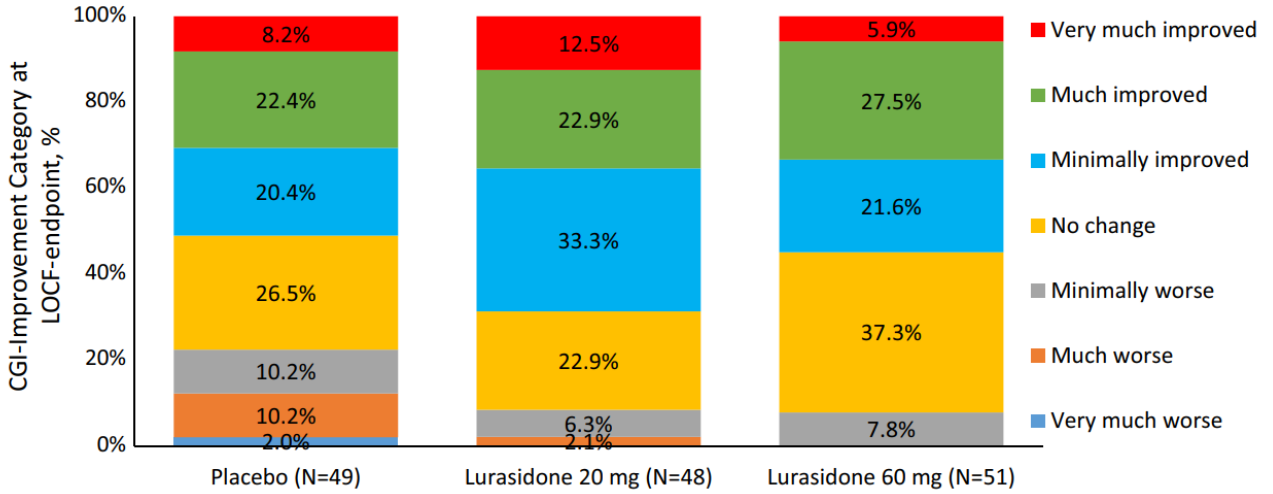
# Atypical Antipsychotics: Lurasidone in Autism

- Randomized, double-blind, placebo-controlled study evaluated lurasidone (20 mg or 60 mg) in children with ASD and irritability (n = 150)
- No difference at 6 weeks between either dose of lurasidone and primary endpoint (change in ABC Irritability scale)
- Did see improvement at endpoint on CGI-I scale for lurasidone 20 mg group compared to placebo, but not for 60mg group

Loebel A et al. J Autism Dev Disord 2016;46(4):1153-63.

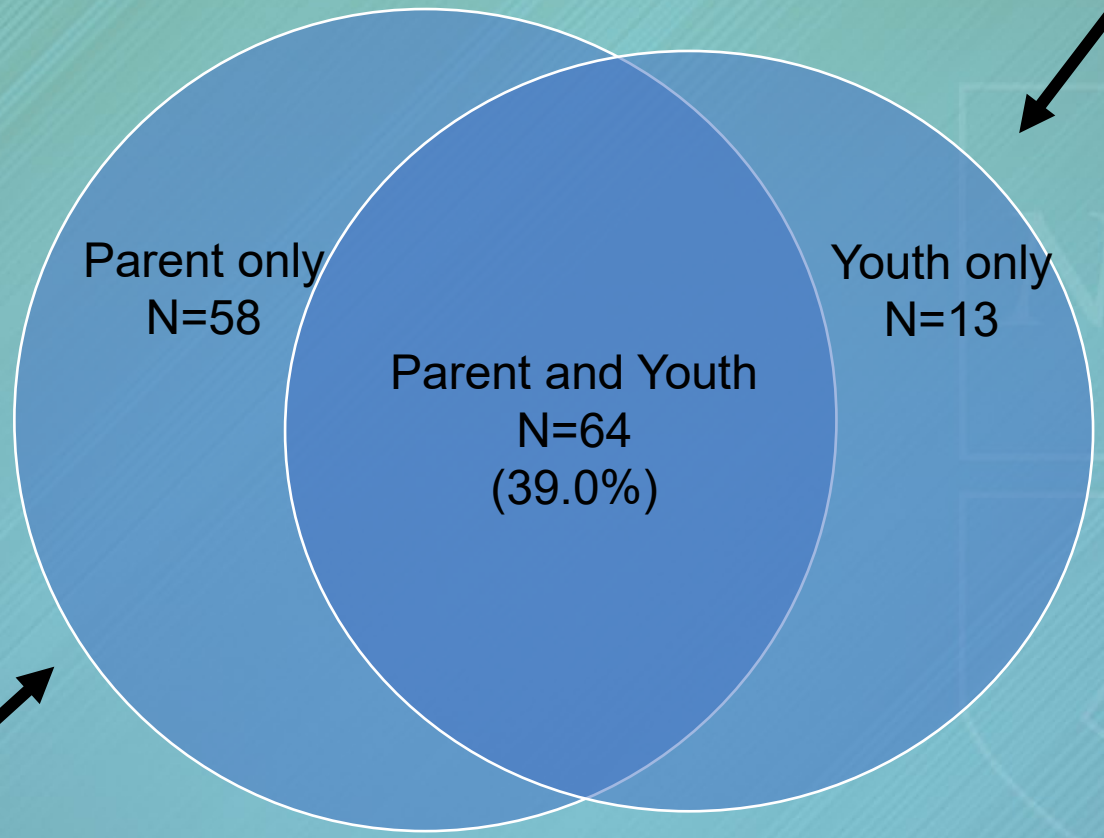
# Change in Irritability and CGI-I




Loebel A et al. J Autism Dev Disord 2016;46(4):1153-63.

# Parent and Youth Irritability Ratings in MDD (n=164)




77 (47.0%) youth report mod. to severe irritability (QIDS-A ≥2).

122 (74.4%) parents report mod. to severe irritability (QIDS-A ≥2).

R01 MH39188 (PI: Emslie, Kennard)

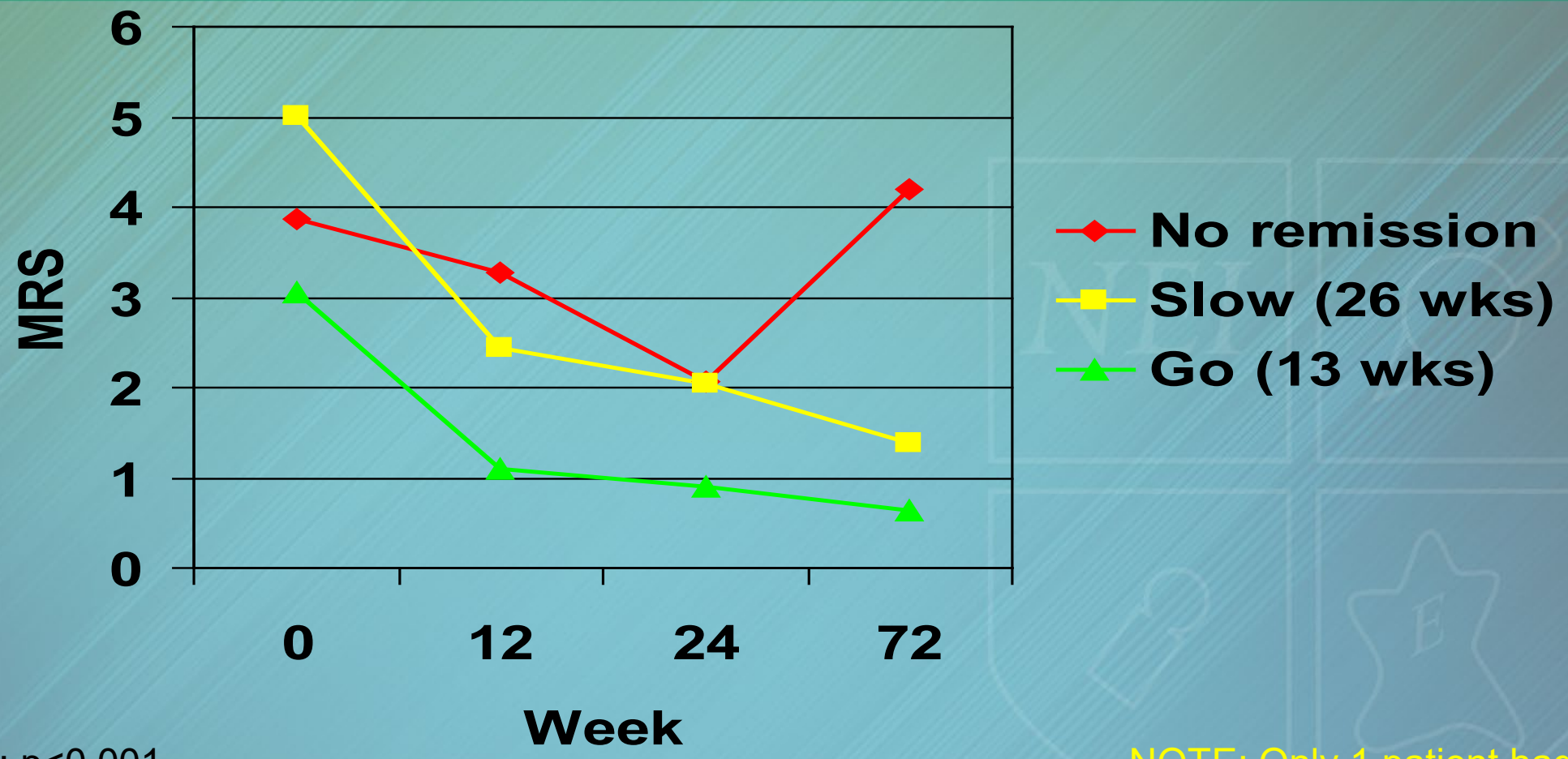
# Irritability
# CDRS-R Item 8 ≥ 4

| MDD Trial | Irritability % |
|---|---|
| Fluoxetine trials (n=315) | 78.4% |
| TADS (n=439) | 80.9% |
| Relapse Prevention (n=173) | 88.4% |
| TORDIA (n=334) | 79.3% |
| TASA (n=124) | 53.2% |

# Irritability by Rating Scale (TORDIA sample; n=334)

- CDRS-R
  - None or very minimal: 6.6%
  - Mild: 13.8%
  - Moderate to Severe: 79.3%
- MRS
  - None or very minimal: 62.3%
  - Mild: 19.1%
  - Moderate to Severe: 18.5%

# Mania Rating Scale (MRS) and Trajectories




SLOW*LnWeek: p<0.001
GO*LnWeek: p=0.04

NOTE: Only 1 patient had hypomania in first 12 weeks

Maalouf FT et al. J Affect Disord 2012;138(1-2):86-95.

# Bipolar Aggression and Irritability

- Seen in mania/mixed, depressive, and euthymic phases
- Track mood with valid rating scale, i.e., YMRS
- If in midst of mood episode optimize response and ensure adherence
- In head-to-head comparison risperidone>lithium>valproic acid for mania
- Therapy such as FBT may help with symptoms including irritability in youth with bipolar disorder

Patino LR, DelBello MP. Child Adolesc Psychiatr Clin N Am 2021;30(3):561-71.

# Psychotherapy

# Nonpharmacologic Aspects of Treatment

- Maintaining boundaries
- Encouraging structure in life
- Addressing systems problems
- Structured psychotherapy, such as dialectical behavior therapy (DBT)
- Implement behavioral therapies including DBT, correct school placement, and parent support

# Summary

- Aggression like fever is a symptom not a disorder
- Frequently brings children into treatment especially for medication management
- Requires therapy and other interventions as well as medication
- When under good control can dramatically change people's lives

# Posttest Question 1

Which medication is FDA approved for the treatment of aggression and for which disorder?

1. Risperidone and schizophrenia
2. Aripiprazole and autism
3. Methylphenidate and ADHD
4. Fluoxetine and major depression

# Posttest Question 2

Which medication(s) was/were found to be helpful in treating disruptive mood dysregulation disorder (DMDD) symptoms with or without comorbid ADHD?

1. Atomoxetine
2. Methylphenidate
3. Citalopram
4. All of the above

# Posttest Question 3

Which medication has been used in ADHD in conjunction with stimulant and parent training therapy?

1. Clonidine
2. Atomoxetine
3. Risperidone
4. Aripiprazole