# Emerging Issues in the Treatment of Impulsive Aggression in Children and Adolescents

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# Question 1

Clinicians may consider tapering atypical antipsychotic medications in patients showing remission of aggressive symptoms for this duration or longer:

a) 2 weeks

b) 1 month

c) 2 months

d) 3 months

e) 6 months

# Question 2

The TRAAY guidelines suggested that for individuals with slightly prolonged QTc Interval (>450 & < 500 msecs), the first line options include:

a) Repeat EKG and decrease dose of antipsychotic

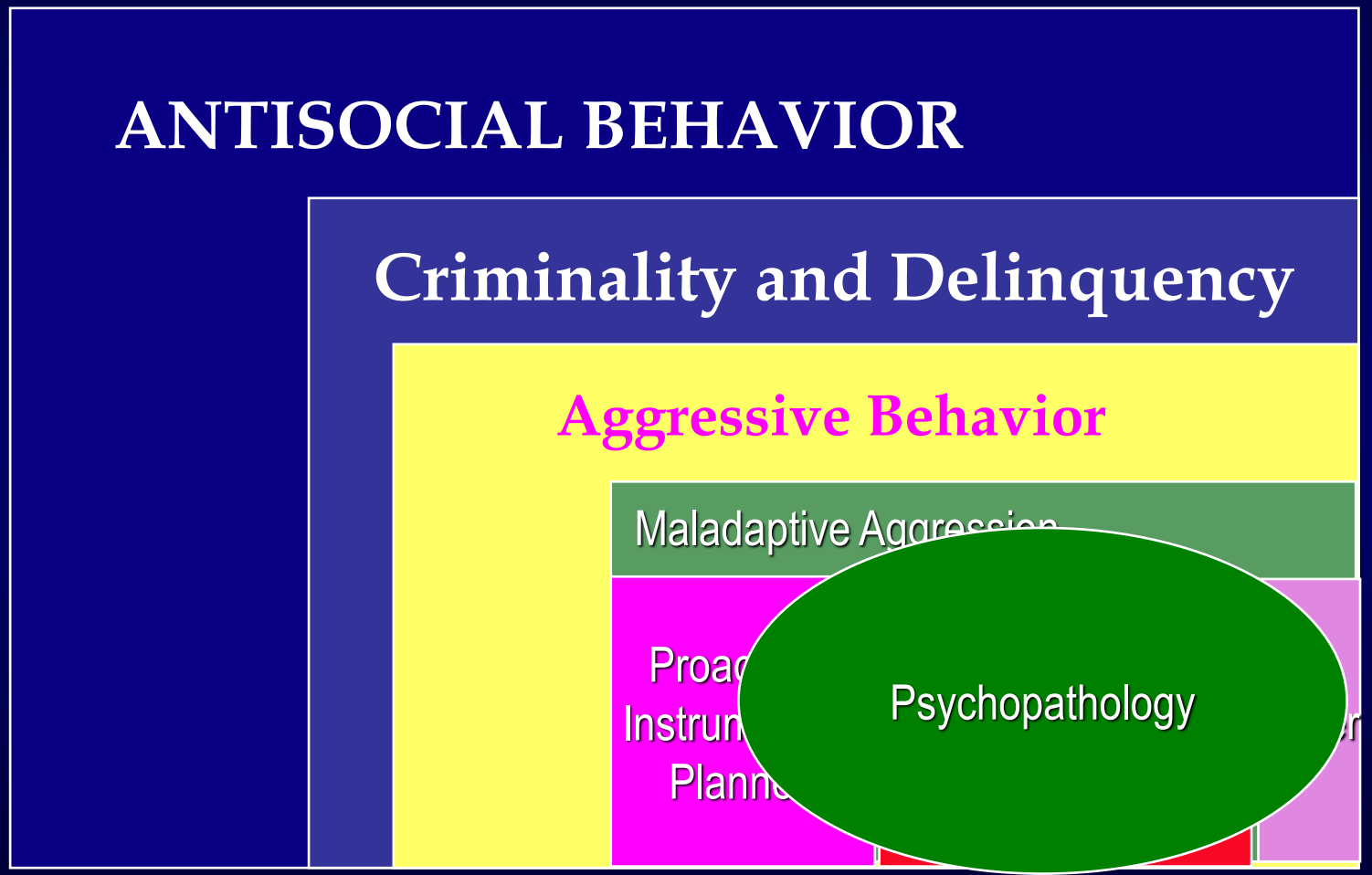
b) Increase dose of antipsychotic

c) Abrupt discontinuation of antipsychotic

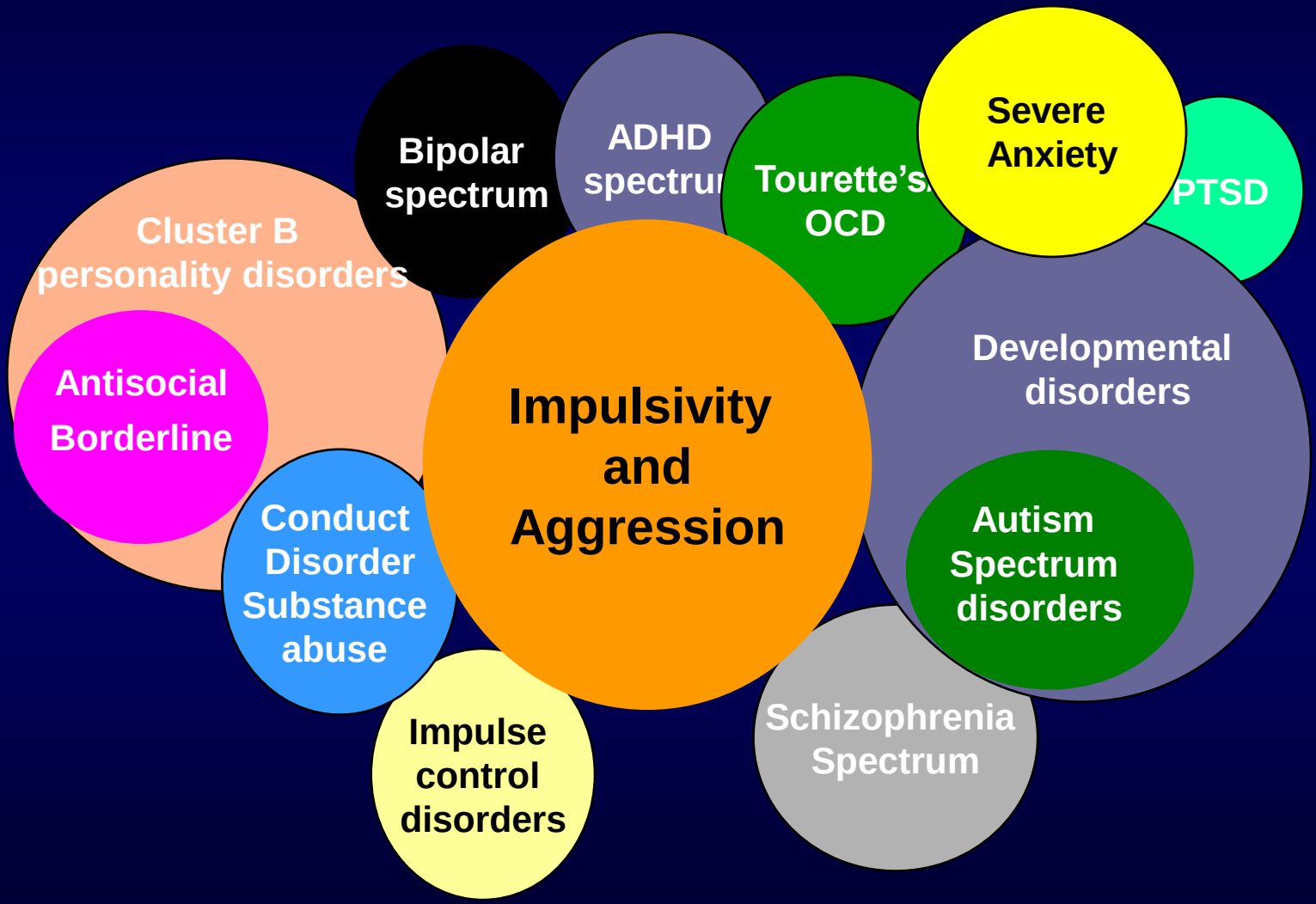
d) Cardiology consult

e) Add antiarrhythmic agent

# Antisocial Behavior, Delinquency and Maladaptive Aggression



# Impulsive-Aggressive Spectrum




Connor, D. In: *Aggression and Antisocial Behavior in Children and Adolescents: Research and Treatment*. New York, NY: Guilford Press; 2002.

# The Neurobiology of Aggression (James Blair et al, 2004)

- **Impulsive (Reactive) and Proactive (Instrumental) Aggression are supported by different neuronal architectures**

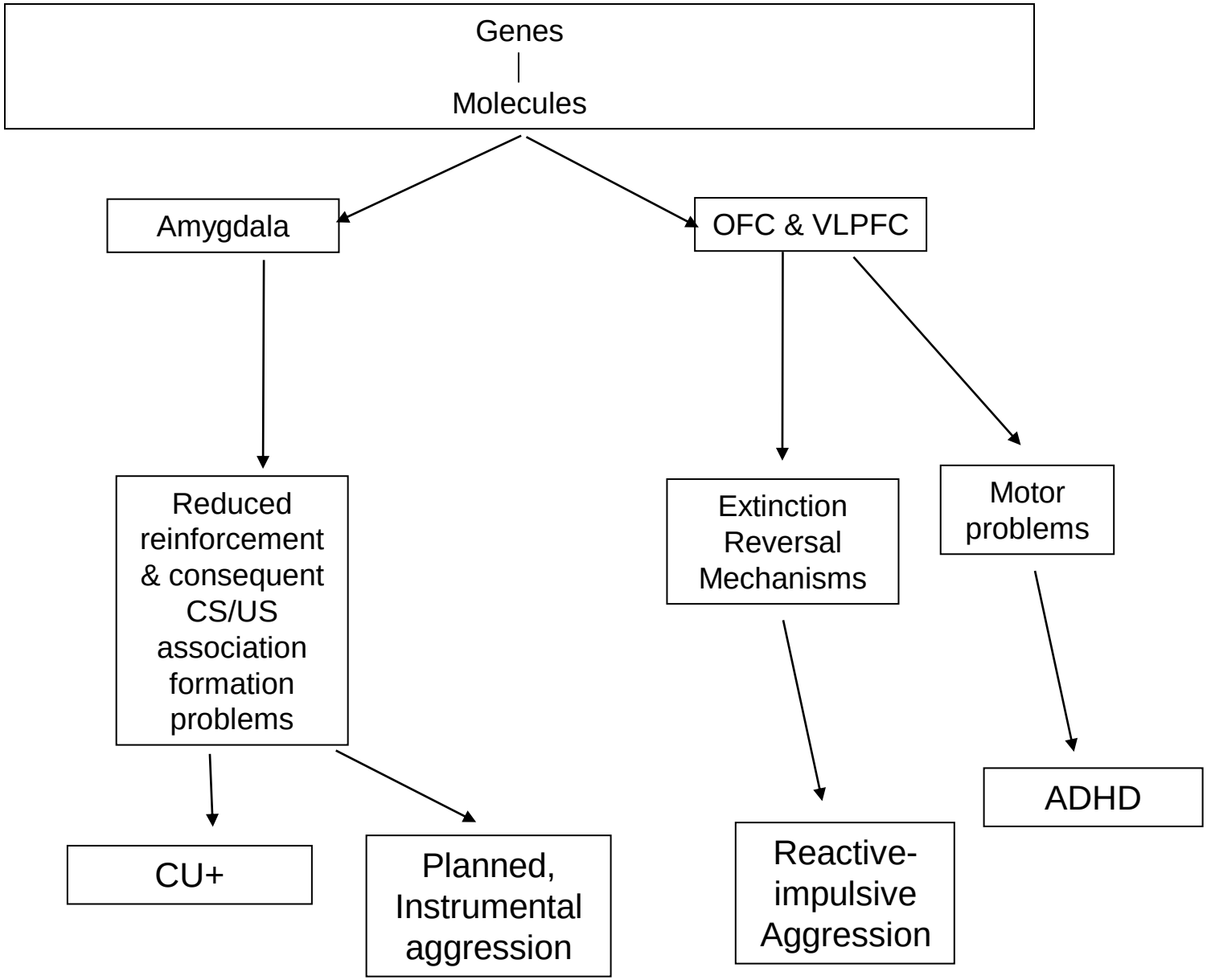
- **Neural circuitry: medial nucleus of amygdala -> medial hypothalamus -> dorsal half of periaqueductal gray. Allows expression of reactive aggression across mammalian species.**

- **Circuitry can become dysfunctional, either through**
  - **problems in the basic neural circuit that responds to threat and allows the expression of reactive aggression (fear and frustration), OR**
  - **problems in the regulatory systems for this circuitry: Functioning of medial/orbital frontal systems involved in the regulation of basic threat circuitry can be compromised.**

- **Impulsive aggression can be the result of excessive activation, deficient restraint (self control) or both.**

- **These problems can arise out of endogenous (genetic vulnerability) or exogenous (abuse or trauma) factors**

# Model of Impulsive Aggression Development



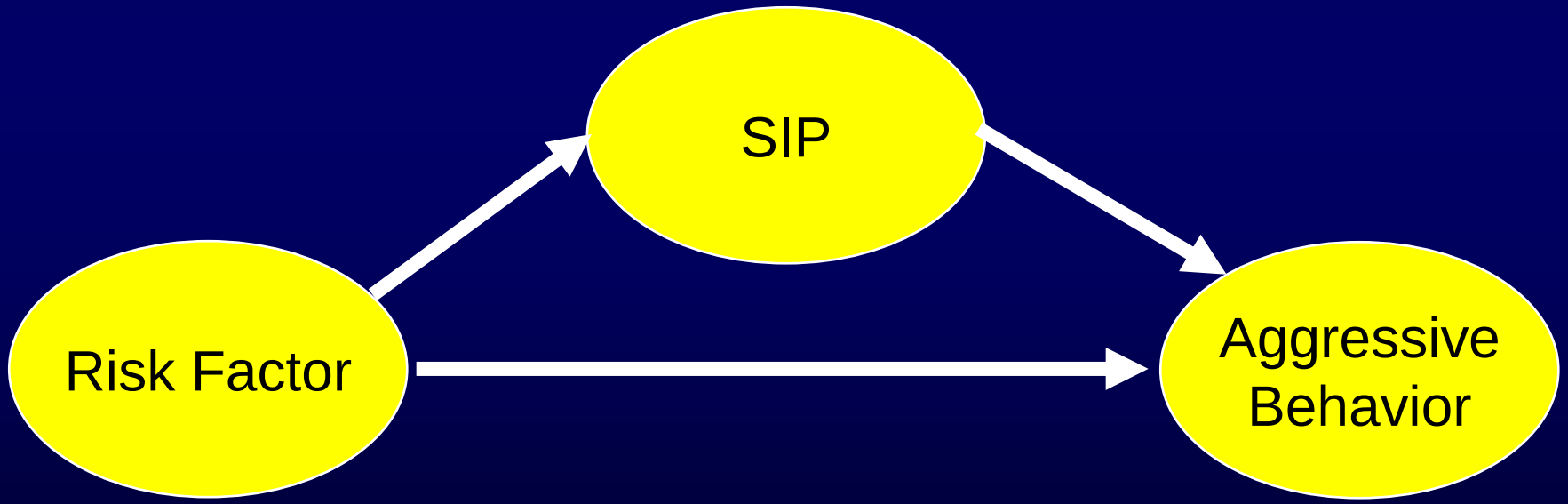
# Environmental Factors

- Experience of aggression as a child
- Witnessing aggression as a child
- Parental dysfunction

# Effect of "Environment" Mediated by Deficits in Social Information Processing

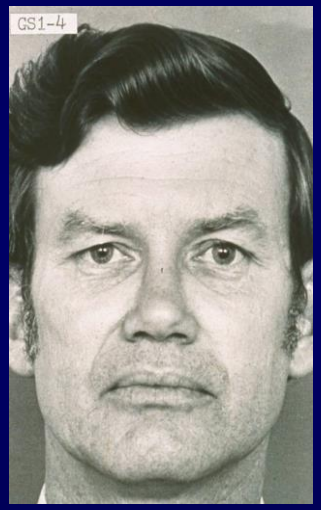
***Aggression in Childhood Associated with Deficits in SIP:***

a. Reduced Encoding of Relevant Social Information
b. Increased Tendency for Hostile Attributions




**Aggression in Childhood, etc.**

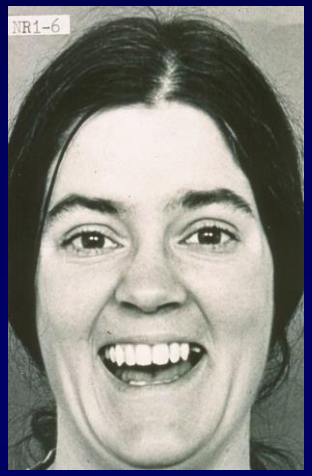
# Assessment of Attributional Tendencies in the "Lab"



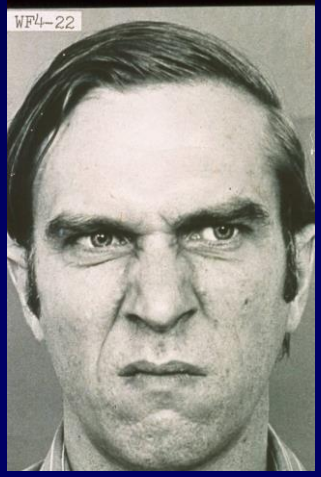

( NEUTRAL )

What Emotion is on this Face?

HAPPY



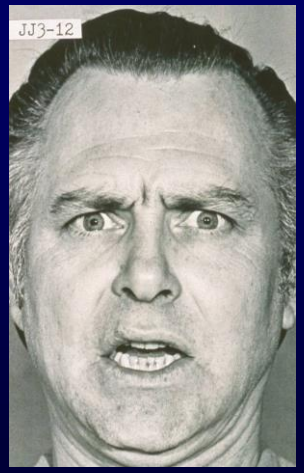

DISGUST





SURPRISE


FEAR




ANGER

# Neuro-Biological Factors

- Dysfunction of Central 5-HT
- Dysfunction of other Central Systems
- Social-Emotional Information Processing

# Correlates: Reactive (Impulsive) and Proactive Aggression ( Dodge K, Lochman JE, Harnish JD et al, 1997)

- **Reactive (Impulsive):**
- Early onset (4.5 ys)
- Physical Abuse in 21%
- Poor peer relations
- Inadequate problem solving patterns

- **Proactive:**
- Later onset ( 6.5)
- No physical Abuse
- Aggressive Models in family
- Attributes positive valency to aggression

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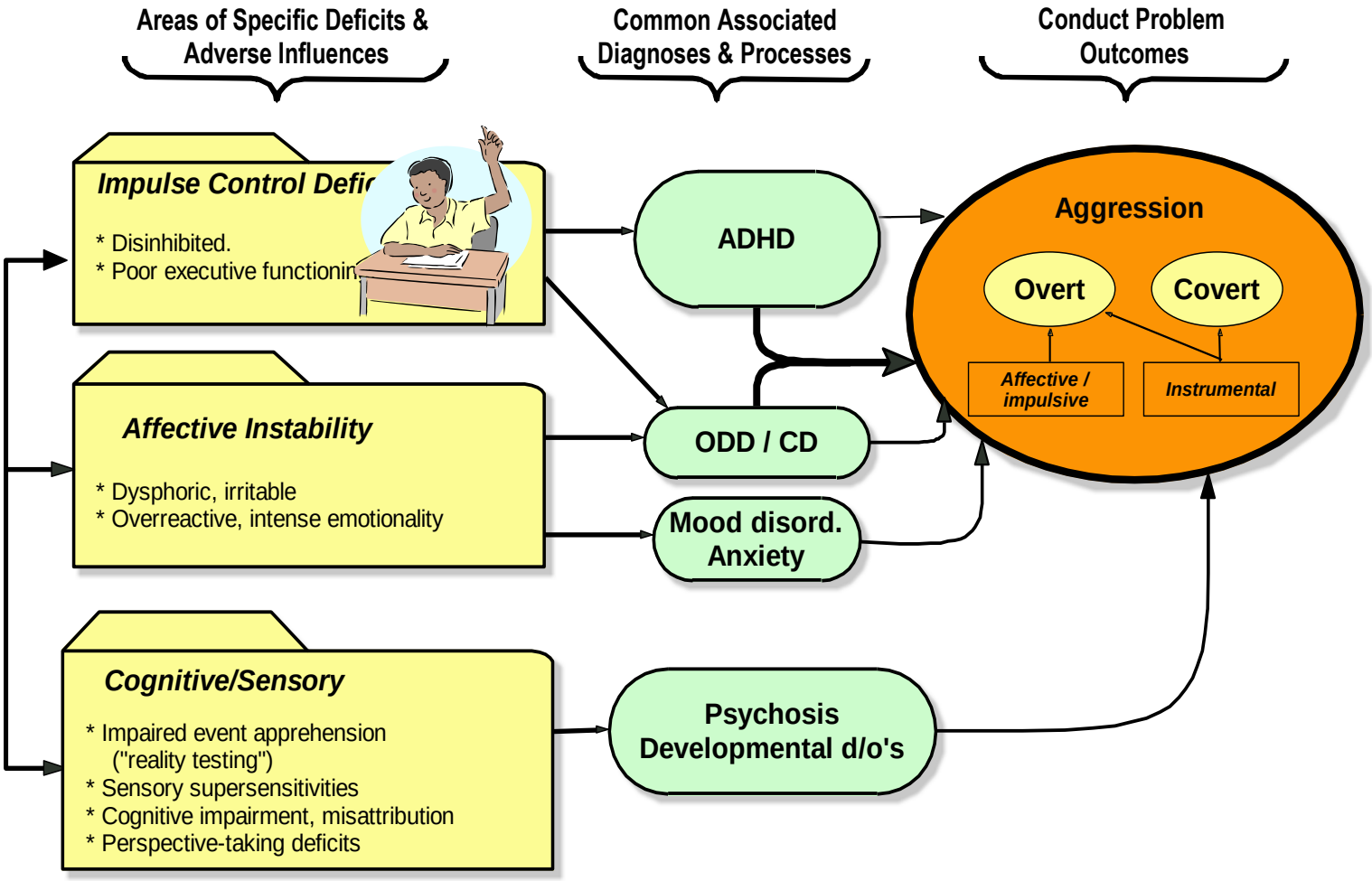
# Main Diatheses for Aggressive Behavior

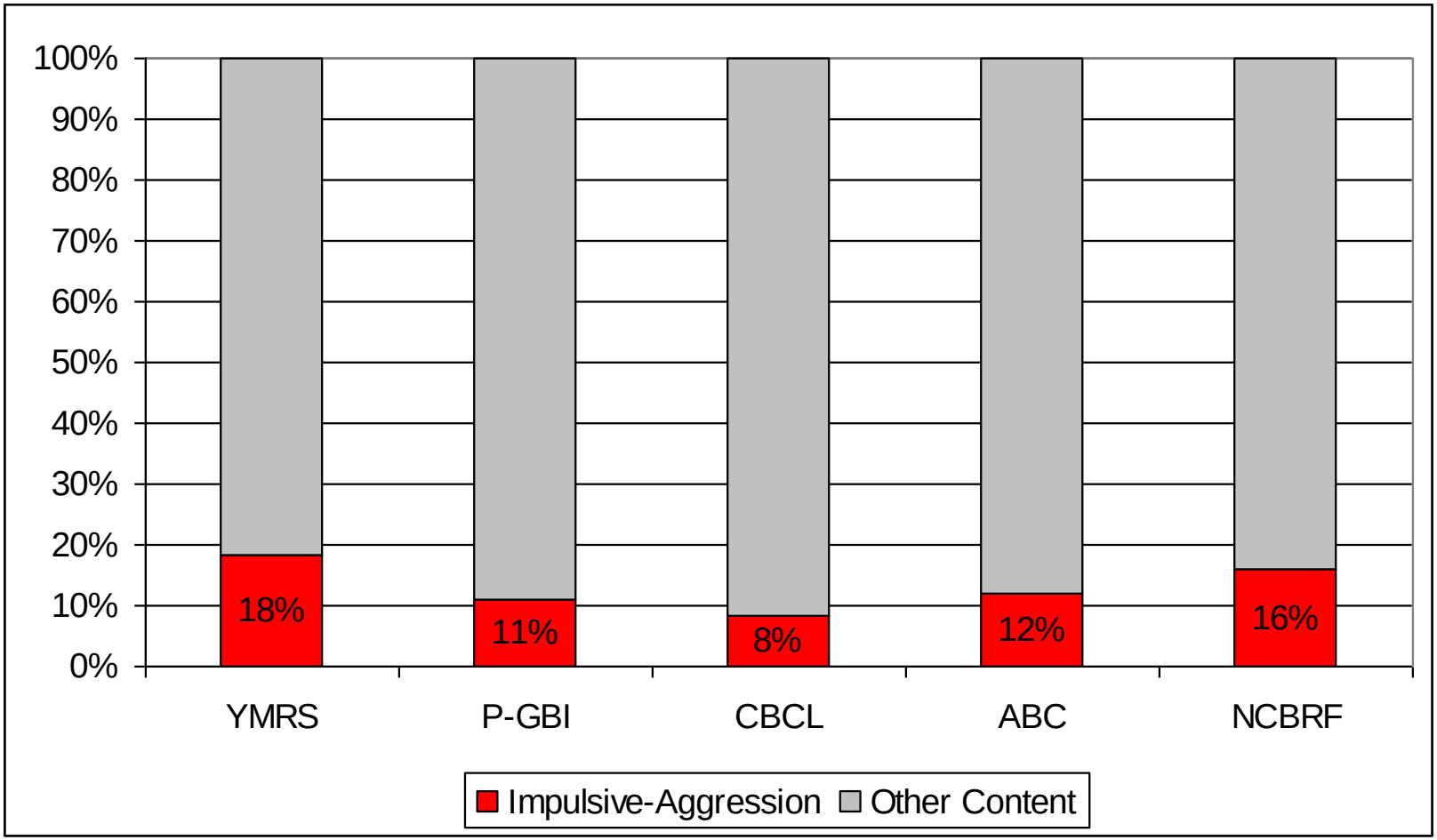


# Can We Reliably Identify It? Internal Consistency – Alpha Youngstrom, 2004

- P-GBI 8 items: $\alpha$ = .87
- A-GBI 8 items: $\alpha$ = .88
- YMRS 2 items: $\alpha$ = .90
- CBCL 10 items: $\alpha$ = .91

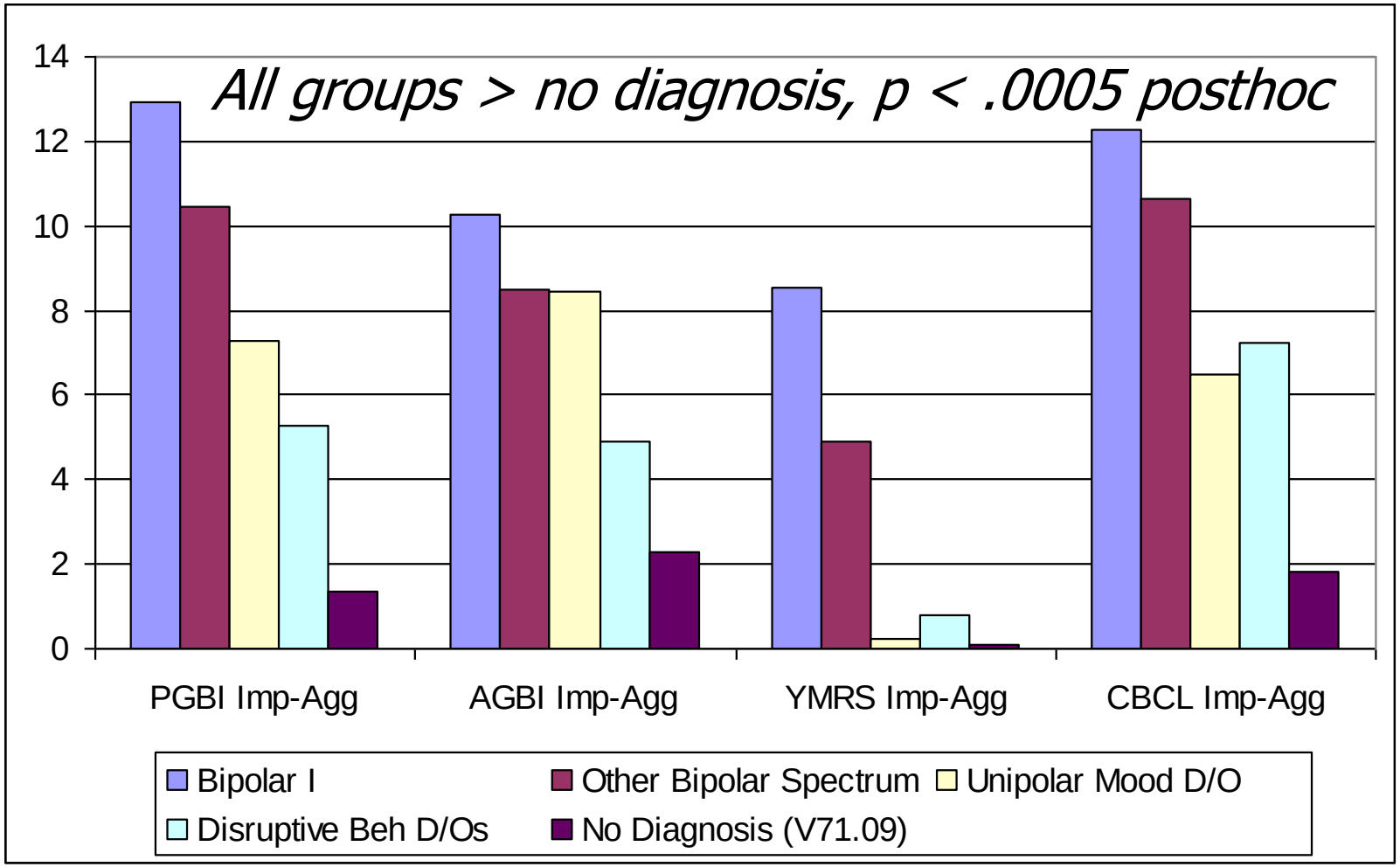
Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007

# Small Subset of Items Across Measures



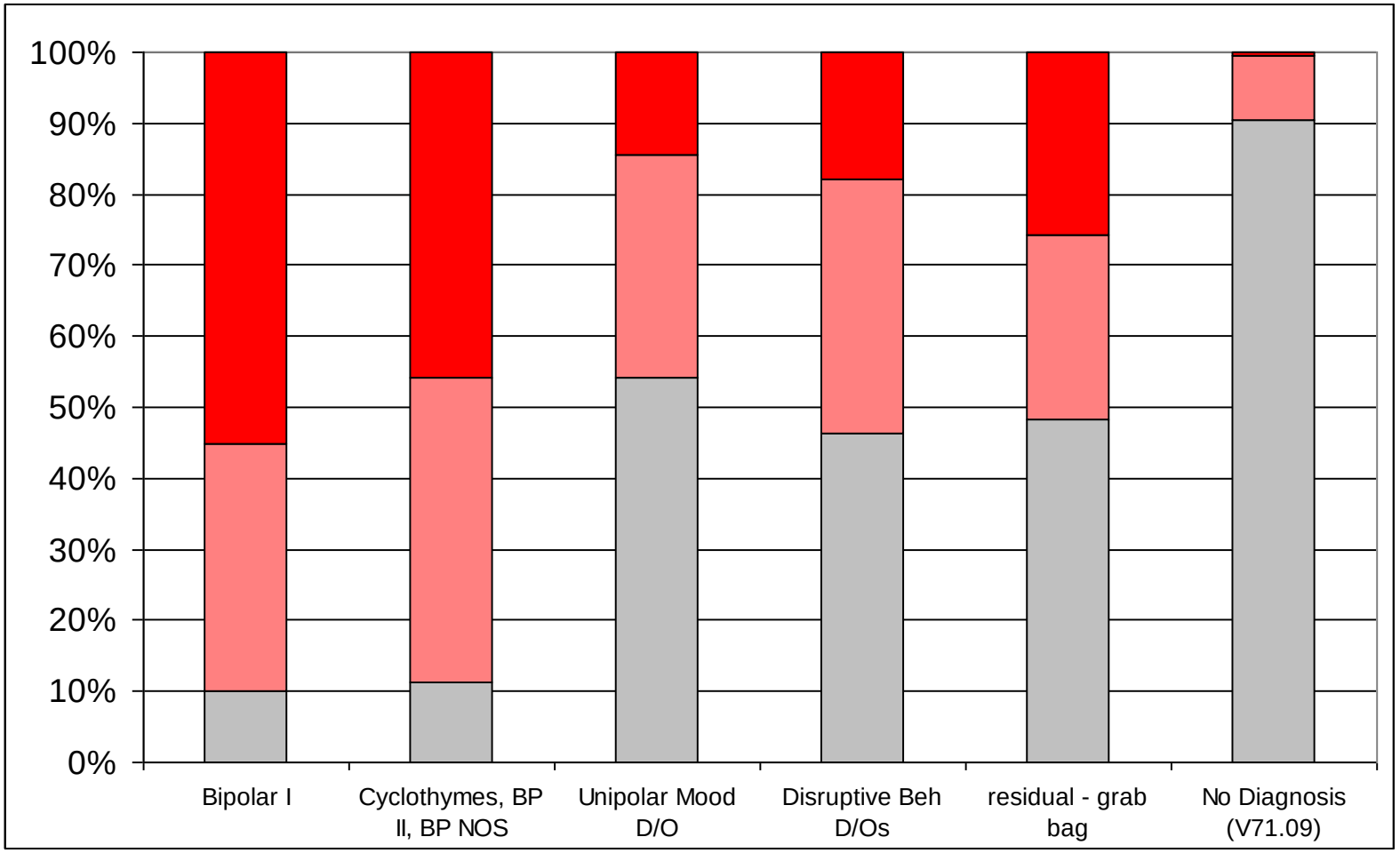

Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007

# Bipolar, ADHD, Unipolar all show significant elevations of Imp-Agg




Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007

# Impulsive Aggression occurs in many cases in all diagnoses studied

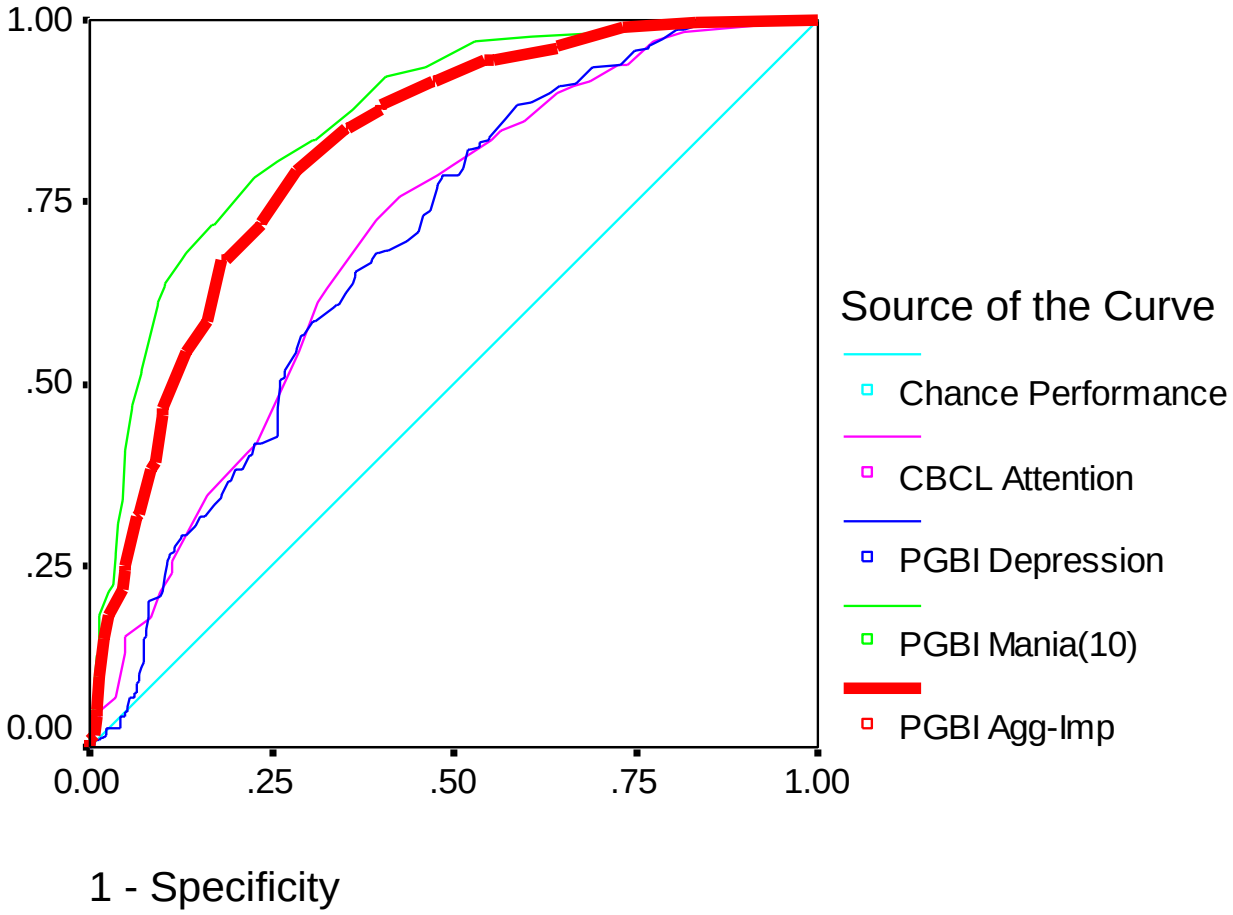



CBCL Item Aggression Profiles

**Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007**

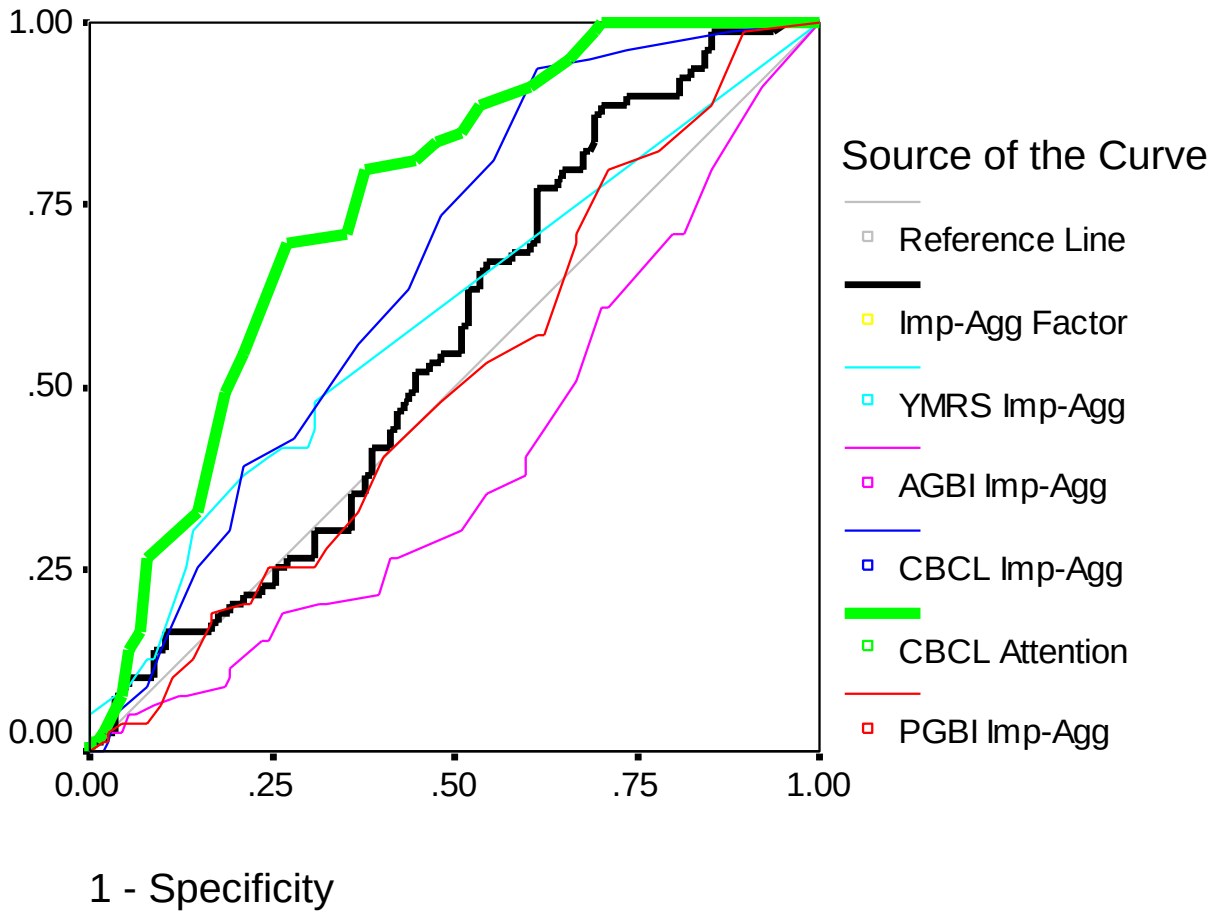
the REACH institute

# Bipolar Disorder – Imp-Agg discriminates less than manic sx



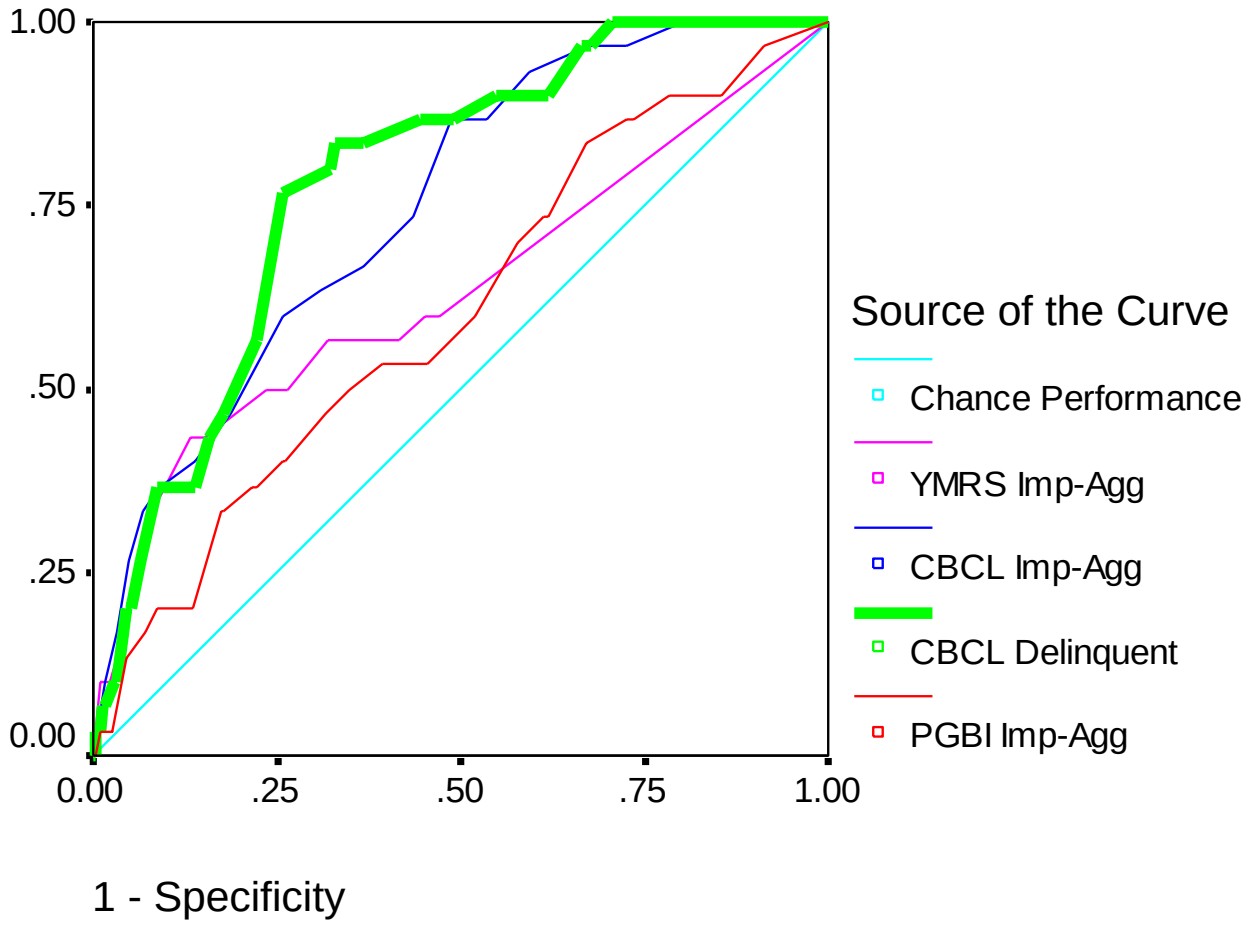

Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007

# ADHD: Imp-Agg Occurs Often, but not specific to condition



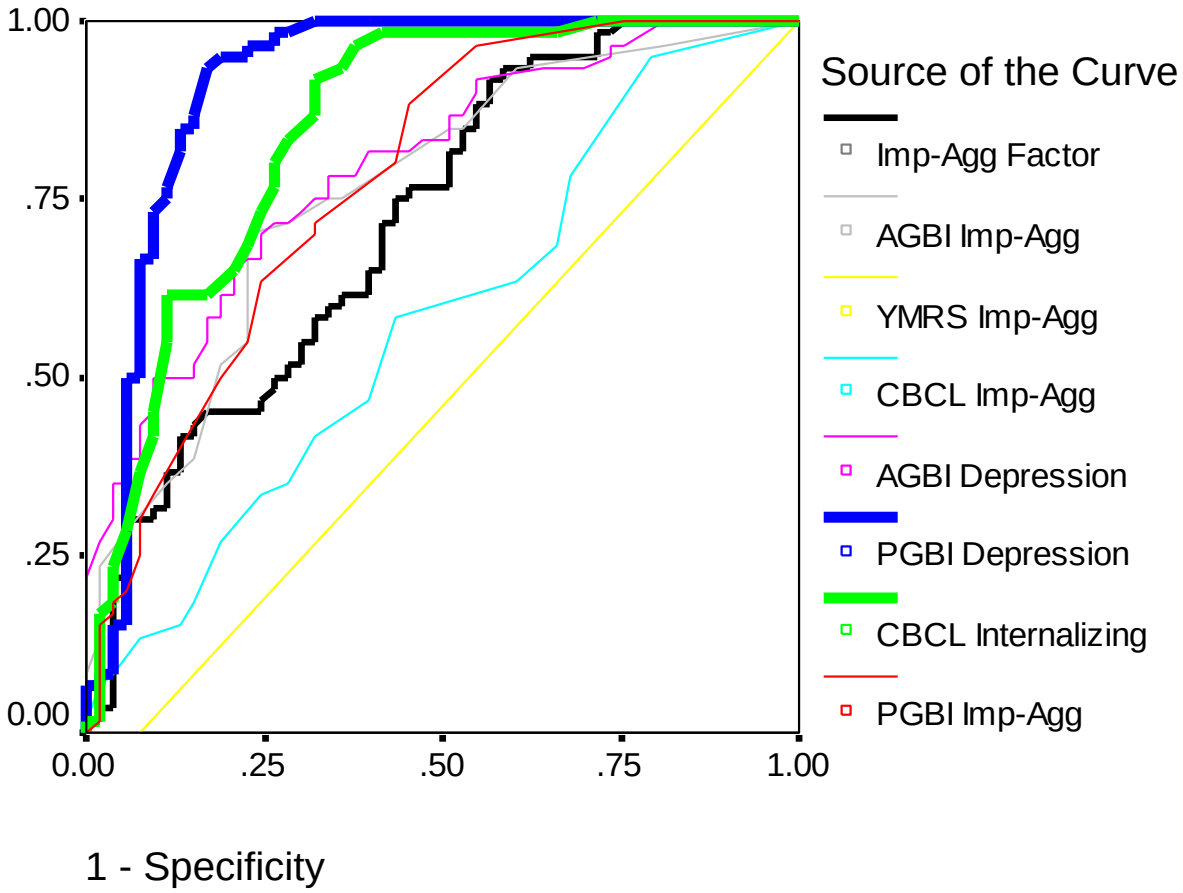

**Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007**

# Conduct Disorder: High levels of Imp-Agg, but Delinquency Higher




Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007

# Imp-Agg also appears in Unipolar Depression




**Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007**

# Conclusions

- Impulsive Aggression important construct in childhood psychopathology
  - Clinical phenomenon – not just normal child behavior
- Can be measured
  - Embedded in existing instruments
  - Can be reliably identified & extracted
  - Good reliability for new subscales
- High mean scores on Impulsive Aggression measures across diagnoses
  - Fairly sensitive marker of illness
- Kids with high levels (LCA) show up across diagnoses
  - Not a specific marker, even for bipolar or conduct disorders
- Not as diagnostic of any condition as are core sx of the condition
  - E.g., lots of aggression in bipolar, but bipolar better identified by other manic sx
- Treatable – sensitive marker, but may track differently from other symptoms



**Jensen, Youngstrom, Steiner, et al., JAACAP 46:309-322, 2007**

# Medications Commonly Used for the Treatment of Aggression in Clinical Practice

- Antipsychotics (DA blockade)
- Anticonvulsants (GABA agonism, glutamate antagonism)
- Stimulants (increase in RAS system)
- SSRI's ( 5 HT increase)
- Anxiolytics (increase in GABAergic transmission)
- Alpha agonists and Beta Blockers (reduction in NA activity)
- Sedatives (sedation)
- Connor et al, 1997; Pappadopulos et al., 2003: 75% of inpt/residential patients receive pharmacotherapy for aggression; 40% two or more meds, antipsychotics common regardless of diagnosis.

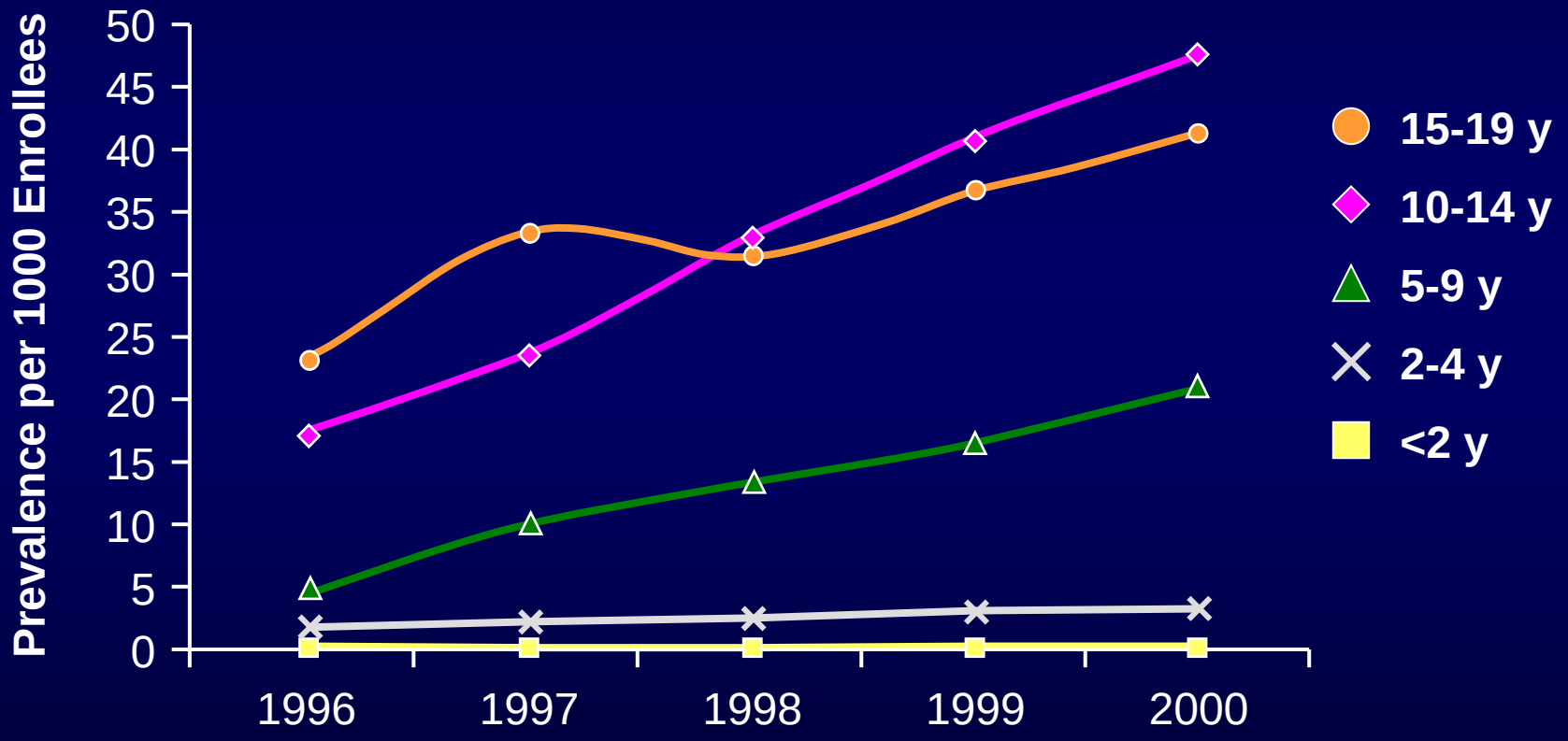
# Impulsive Aggression in C & As: Critical Treatment Issues

- Aggressive behavior is the most common reason for psychiatric referrals
- Aggression complicates treatment and leads to poorer outcomes
- Aggression leads to frequent use of atypical antipsychotics and multiple medications
- There is a lack of controlled trials to inform physicians' prescribing practices

Pappadopulos EA, Jensen PS, Schur SB, et al (2002). *Schizophr Bull* 28(1):111-121.

# Antipsychotic Use Is Increasing in Children and Adolescents

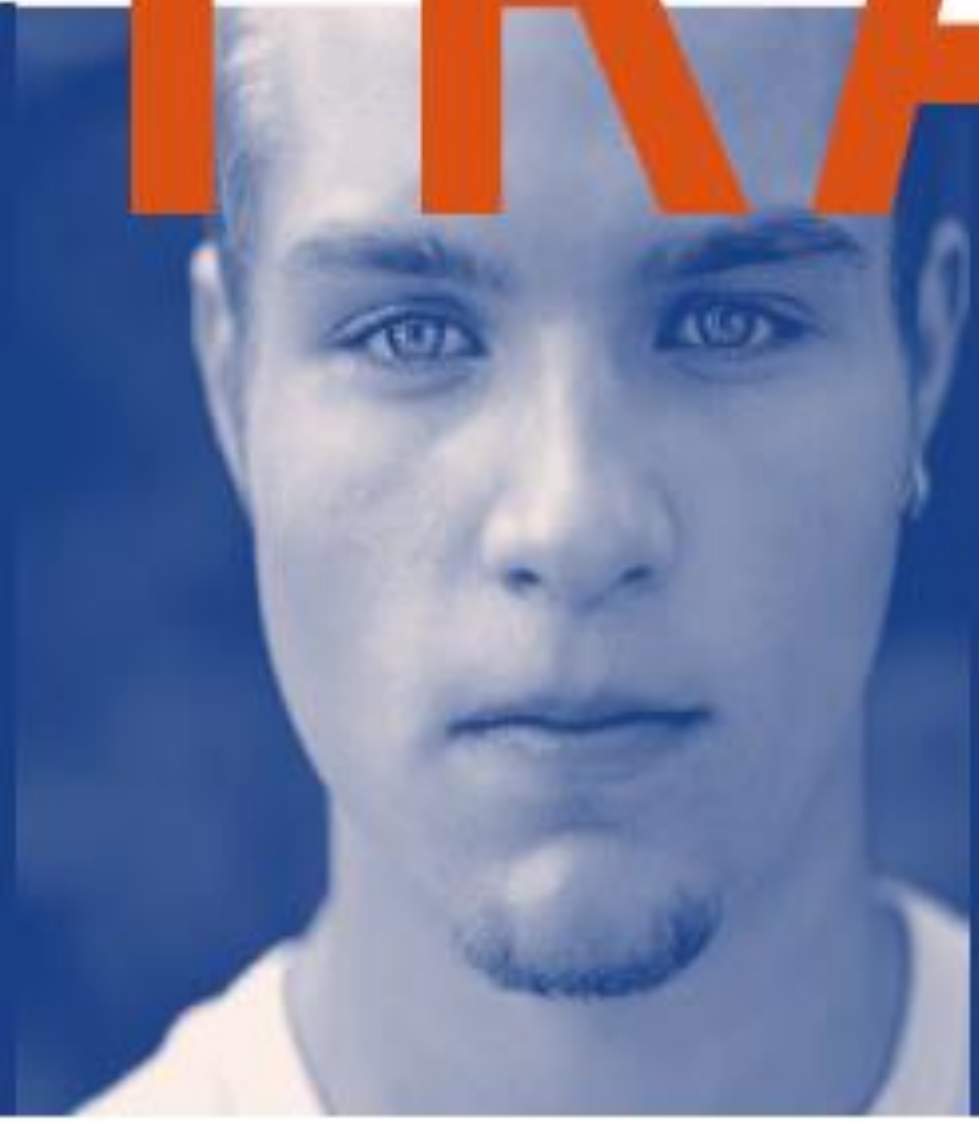
**Age-specific prevalence rates of total antipsychotic use (1996-2000) based on analysis of Texas Medicaid claims**




**(N=28,540)**

Patel NC, Sanchez RJ, Johnsrud MT, et al (2002). *J Child Adolesc Psychopharmacol* 12(3):221-229.

# TRAAY



## Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth

Version
12/8/04

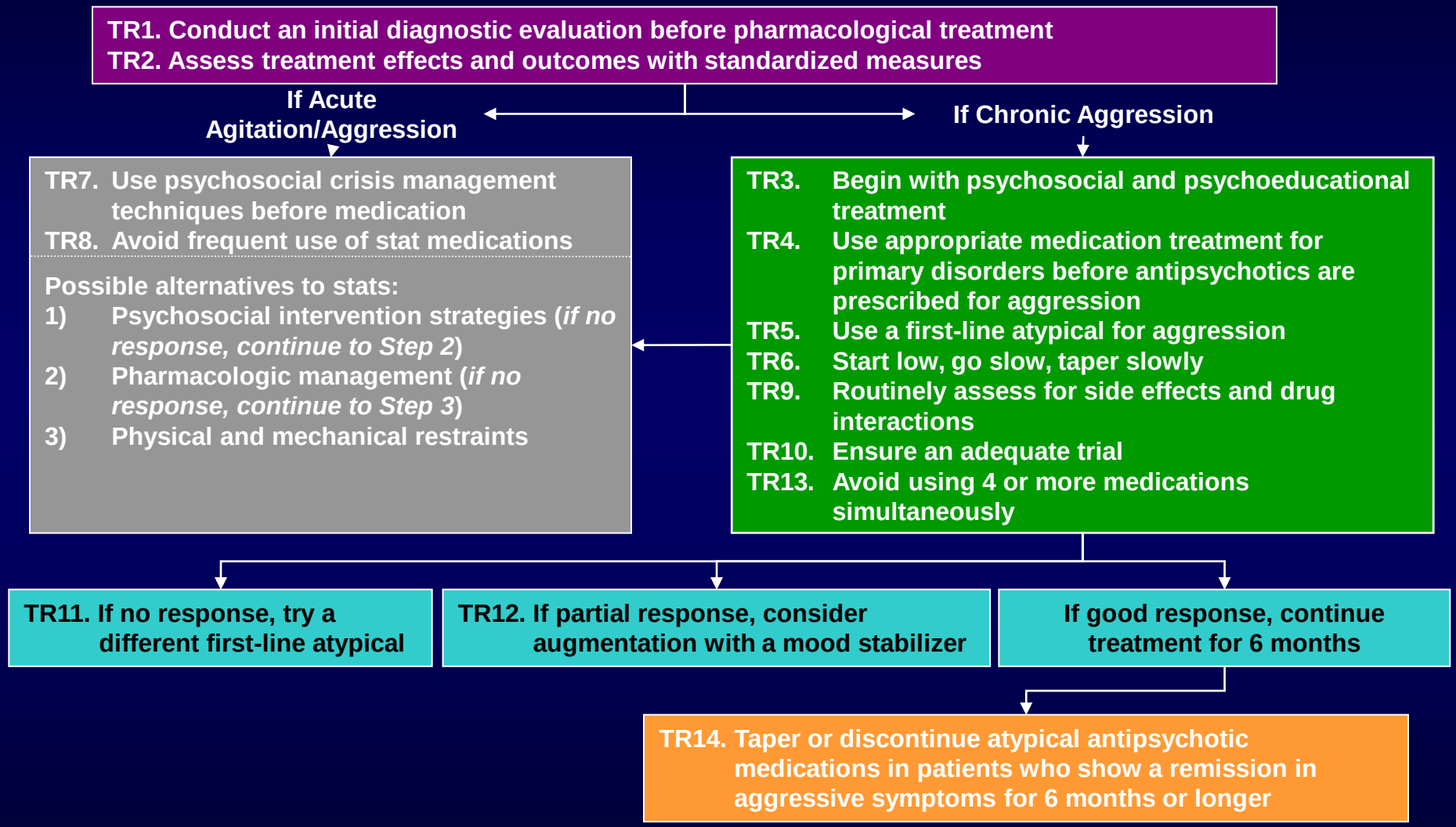
# Selected Studies of Disruptive Behavior Disorders With Aggression in Children/Adolescents

- **Randomized studies**
  - Aman, et al (2002)
  - Findling, et al (2000)
  - Snyder, et al (2002)
  - Buitelaar, et al (2001)
  - Van Bellinghen, De Troch (2001)
- **Nonrandomized, long-term studies**
  - Turgay, et al (2002)
  - Findling, et al (2004)

# Short-Term Randomized Trials for Aggression

| Study | *Subjects* Diagnosis | Duration & Dose range | Results |
|---|---|---|---|
| Aman et al, 2002 | *n=118, 5-12 years*<br>•DBD/ Subaverage intelligence | •6 weeks<br>•oral **risperidone** 0.02-0.06 mg/kg/day | • Risperidone more effective than placebo.<br>• AE: headache, somnolence |
| Snyder et al, 2002 | *n=110, 5-12 years, IQ 36-84*<br>• DBD, NCBRF score ≥ 24<br>• 80% w/ comorbid ADHD | •1 week (SB) then 6 weeks (DB)<br>•**risperidone** 0.02-0.06 mg/kg/day | • Risperidone superior to placebo<br>• AE: somnolence, headache, appetite ↑, dyspepsia. |
| Van Bellinghen et al, 2001 | *n=13, 6-14 years, IQ 66-85*<br>•behavioral disturbance | •4 weeks<br>•**risperidone** ≤ .01 mg/kg/day | • Risperidone superior to placebo |
| Findling et al, 2000 | *n=20, 5-15 years*<br>•CD/ Moderate severity (CGI) | •10 weeks<br>• **risperidone** <50 kg, ≤ 1.5 .mg/kg/day;>50 kg, ≤ 3 mg/kg/day | •Risperidone superior to placebo<br>• No noted EPS |

# Flow Chart Depicting the Systematic Application of the TRAAY




Pappadopulos EA, MacIntyre II JC, Crismon ML, et al (2003). *J Am Acad Child Adolesc Psychiatry* 42(2):145-161.

# Texas CMAP 2000

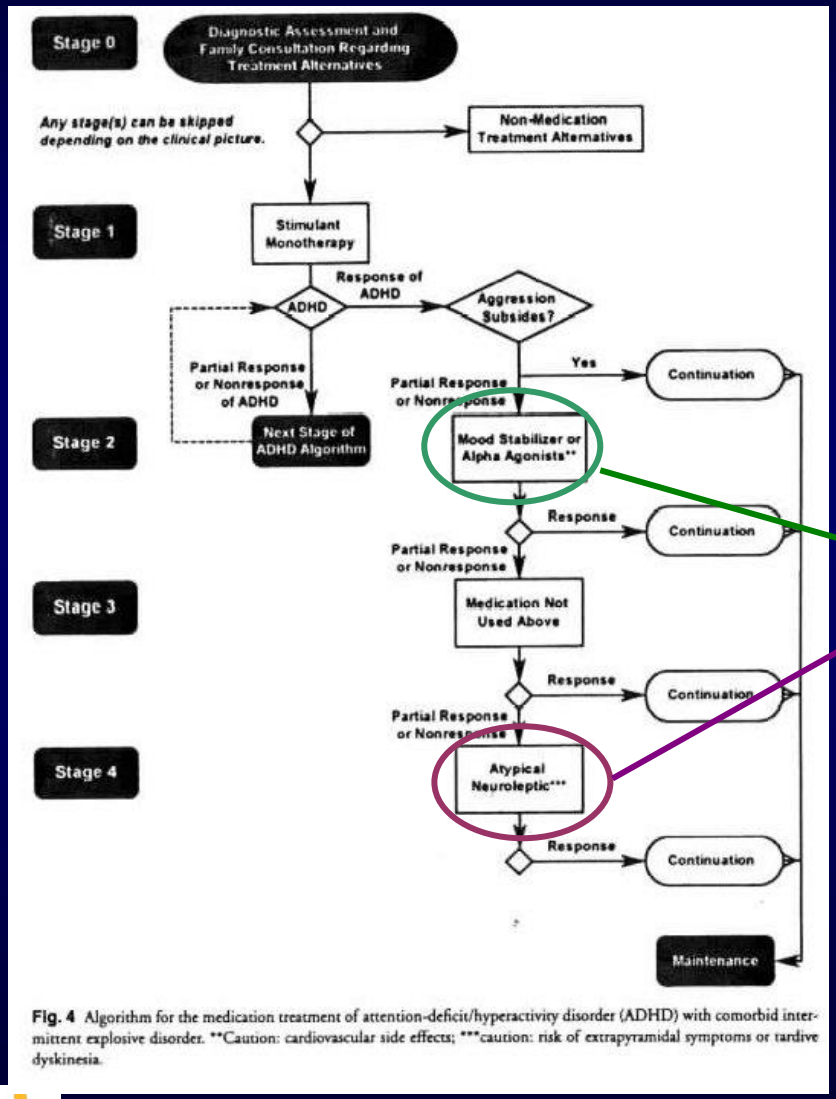
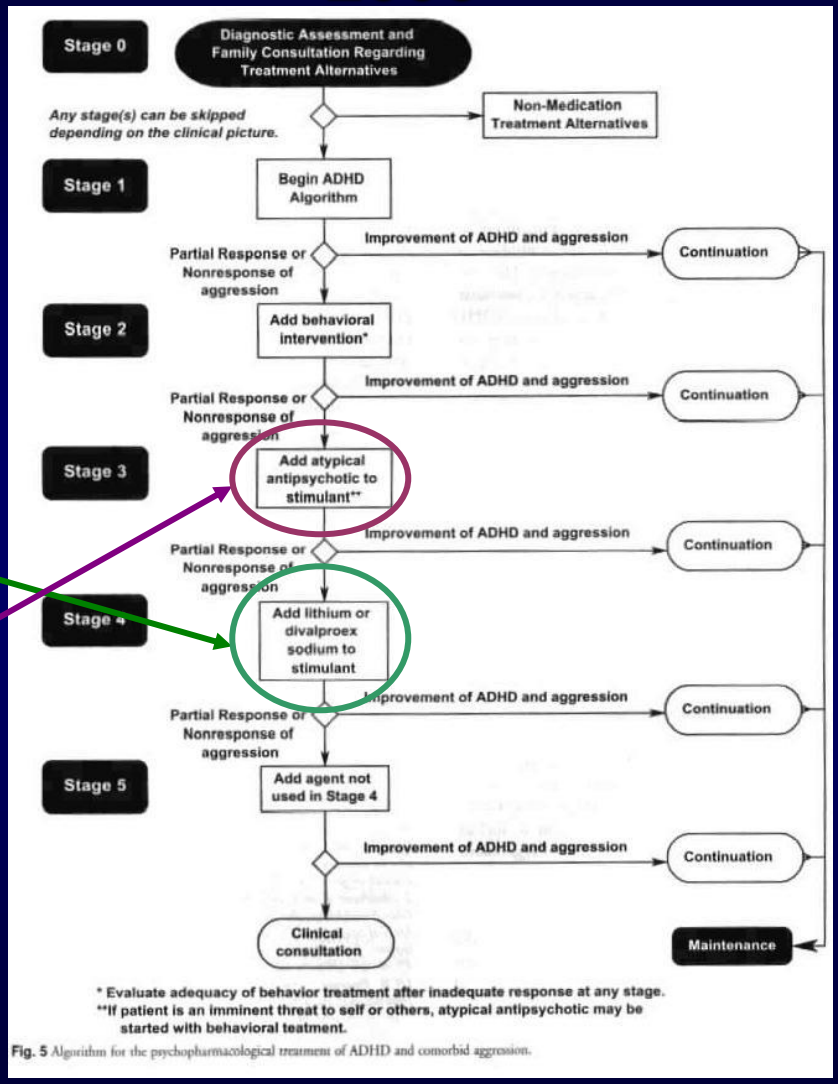



**Fig. 4** Algorithm for the medication treatment of attention-deficit/hyperactivity disorder (ADHD) with comorbid intermittent explosive disorder. **Caution: cardiovascular side effects; ***caution: risk of extrapyramidal symptoms or tardive dyskinesia.

# Texas CMAP 2006




* Evaluate adequacy of behavior treatment after inadequate response at any stage.
**If patient is an imminent threat to self or others, atypical antipsychotic may be started with behavioral teatment.

**Fig. 5** Algorithm for the psychopharmacological treatment of ADHD and comorbid aggression.

# Center for Education and Research Therapeutics in Behavioral Health

## Treatment Recommendations for the Outpatient Management of Behavior Problems in Youth

***Assessment and Diagnosis***
- Engage patient and parents during initial evaluation.
- Conduct a thorough initial evaluation and diagnostic work-up before pharmacological treatment.
- Assess treatment effects and outcomes with standardized measures.

***Initial Management and Treatment Planning***
- Provide psychoeducation for patients and families and set realistic expectations about treatment.
- Partner with patient and family in developing an acceptable treatment plan.
- Help the family establish community supports.

**If Acute Agitation/Aggression**

- Conduct risk assessment and if necessary, consider referral to psychiatrist or ER evaluation.
- Help parents/family prepare a safety plan and connect with community resources and supports
- Consider prescribing medication at the first visit depending on:
  - Potential harm to self or others
  - History of severe impulsive or aggressive behavior
  - Previous positive response to medication treatments.

**If Chronic Aggression**

***Psychosocial Interventions***

-Provide or assist the family in obtaining evidence-based parent and child skills training.

***Medication Treatment***

-Initial medication treatment should target the underlying disorder(s).

-Where available, follow evidence-based guidelines for primary disorder.

**-Use recommended titration schedule and deliver an adequate medication trial before changing or adding medication.**

**--If needed, consider a first-line atypical antipsychotic for aggression**

-Avoid using more than 2 medications from the same class or greater than 3 medication simultaneously.

***Side Effects Assessment and Management***

**Routinely assess for side effects & medication interactions.**

**-Use structure rating scales to monitor side effects**

**TR11. If no response, try a different first-line atypical**

**TR12. If partial response, consider augmentation with a mood stabilizer**

**If good response, continue treatment for 6 months**

**Taper or discontinue atypical antipsychotic medications in patients who show a remission in aggressive symptoms for 6 months or longer**

# Initial Evaluation Prior to Pharmacologic Treatment

- Comprehensive diagnostic interview with patient and parent/guardian
  - Contact prior treating physician
  - Review treatment records
  - Contact teachers
  - Identify other medications being taken
- Physical examination
- Appropriate laboratory studies

# Assess Treatment Effects and Outcomes

- Even well-trained psychiatrists may be unreliable without standardized symptom/behavior rating scales[1]. Scales should be used to measure severity and frequency of target symptoms (eg, Modified Overt Aggression Scale):
  - Prior to treatment or at baseline evaluation
  - At regular intervals throughout treatment
  - During acute episodes
  - When treatments are changed or discontinued

[1]Piacentini J, Shaffer D, Fisher PW, et al (1993). *J Am Acad Child Adolesc Psychiatry* 32(3): 658-665.
Pappadopulos EA, MacIntyre II JC, Crismon ML, et al (2003). *J Am Acad Child Adolesc Psychiatry* 42(2):145-161.

# THE MODIFIED OVERT AGGRESSION SCALE (MOAS)*

Patient

Rater Date

## INSTRUCTIONS

Rate the patient's aggressive behavior over the past week. Select as many items as are appropriate. Refer to the pocket guide for the full measure.

## SCORING

1) Add items in each category. 2) In scoring summary, multiply sum by weight and add weighted sums for total weighted score. Use this score to track changes in level of aggression over time.

***Verbal Aggression***

_____ **0** No verbal aggression
_____ **1** Shouts angrily, curses mildly, or makes personal insults
_____ **2** Curses viciously, is severely insulting, has temper outbursts
_____ **3** Impulsively threatens violence toward others or self
_____ **4** Threatens violence toward others or self repeatedly or deliberately
_____ **SUM VERBAL AGGRESSION SCORE**

***Aggression Against Property***

_____ **0** No aggression against property
_____ **1** Slams door angrily, rips clothing, urinates on floor
_____ **2** Throws objects down, kicks furniture, defaces walls
_____ **3** Breaks objects, smashes windows
_____ **4** Sets fires, throws objects dangerously
_____ **SUM PROPERTY AGGRESSION SCORE**

***Autoaggression***

_____ **0** No autoaggression
_____ **1** Picks or scratches skin, pulls hair out, hits self (without injury)
_____ **2** Bangs head, hits fists into walls, throws self on floor
_____ **3** Inflicts minor cuts, bruises, burns, or welts on self
_____ **4** Inflicts major injury on self or makes a suicide attempt
_____ **SUM AUTOAGGRESSION SCORE**

***Physical Aggression***

_____ **0** No physical aggression
_____ **1** Makes menacing gestures, swings at people, grabs at clothing
_____ **2** Strikes, pushes, scratches, pulls hair of others (without injury)
_____ **3** Attacks others, causing mild injury (bruises, sprains, welts, etc.)
_____ **4** Attacks others, causing serious injury
_____ **SUM PHYSICAL AGGRESSION SCORE**

| CATEGORY | SUM SCORE | WEIGHTS | WEIGHTED SUM |
|---|---|---|---|
| Verbal Aggression | | X1 | |
| Aggression Against Property | | X2 | |
| Autoaggression | | X3 | |
| Physical Aggression | | X4 | |
| **Total Weighted Score** | | | |

* Modified from Kay SR, Wolkenfelf F, Murrill LM (1988), Profiles of aggression among psychiatric patients: I. nature and prevalence. *Journal of Nervous and Mental Disease 176*:539–546

# Begin With Psychosocial and Educational Interventions

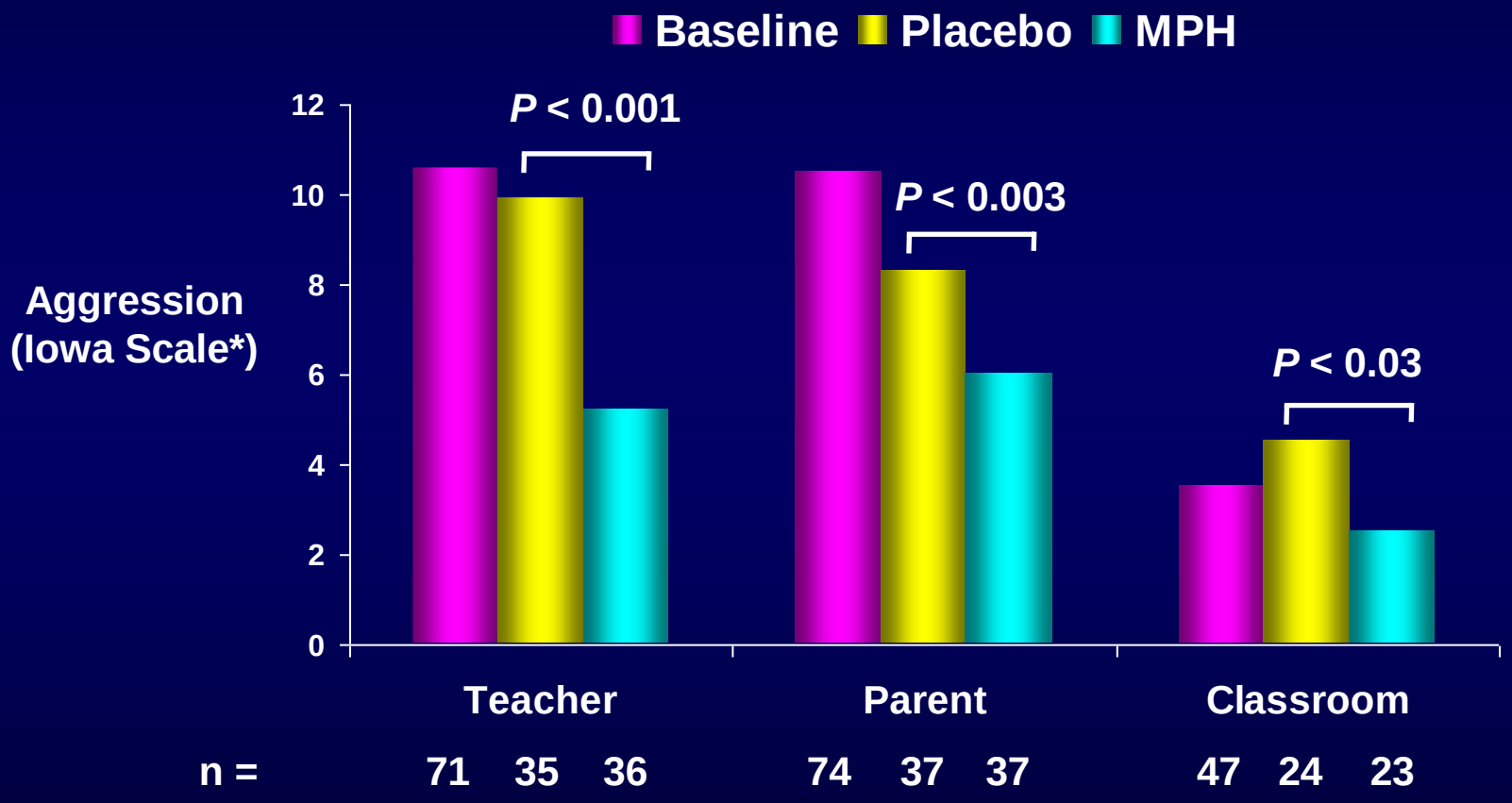
- Initiate psychosocial/behavioral treatment
- Exact therapeutic approach will depend on diagnosis and individual circumstances
- Provide evidence-based (EB) psychosocial treatment or close to it
- Assess patient response
- Continue psychosocial and/or educational therapy even if medication is initiated later to manage aggression

# Pharmacologic Treatment of Primary Disorder

- Choose appropriate pharmacologic agent for primary disorder
  - Accurate diagnosis vital
  - Anticipate potential drug interactions
  - Evaluate potential impact of side effects on individual patient
- Use monotherapy whenever possible to simplify
  - Assessment of treatment response
  - Assessment of side effects
  - Medication regimen

Schur SB et al. *J Am Acad Child Adolesc Psychiatry*. 2003;42:132-144.
Connor. In: *Aggression and Antisocial Behavior in Children and Adolescents: Research and Treatment*. New York, NY: Guilford Press; 2002.

# Methylphenidate in ADHD/CD: Impulsive Aggression



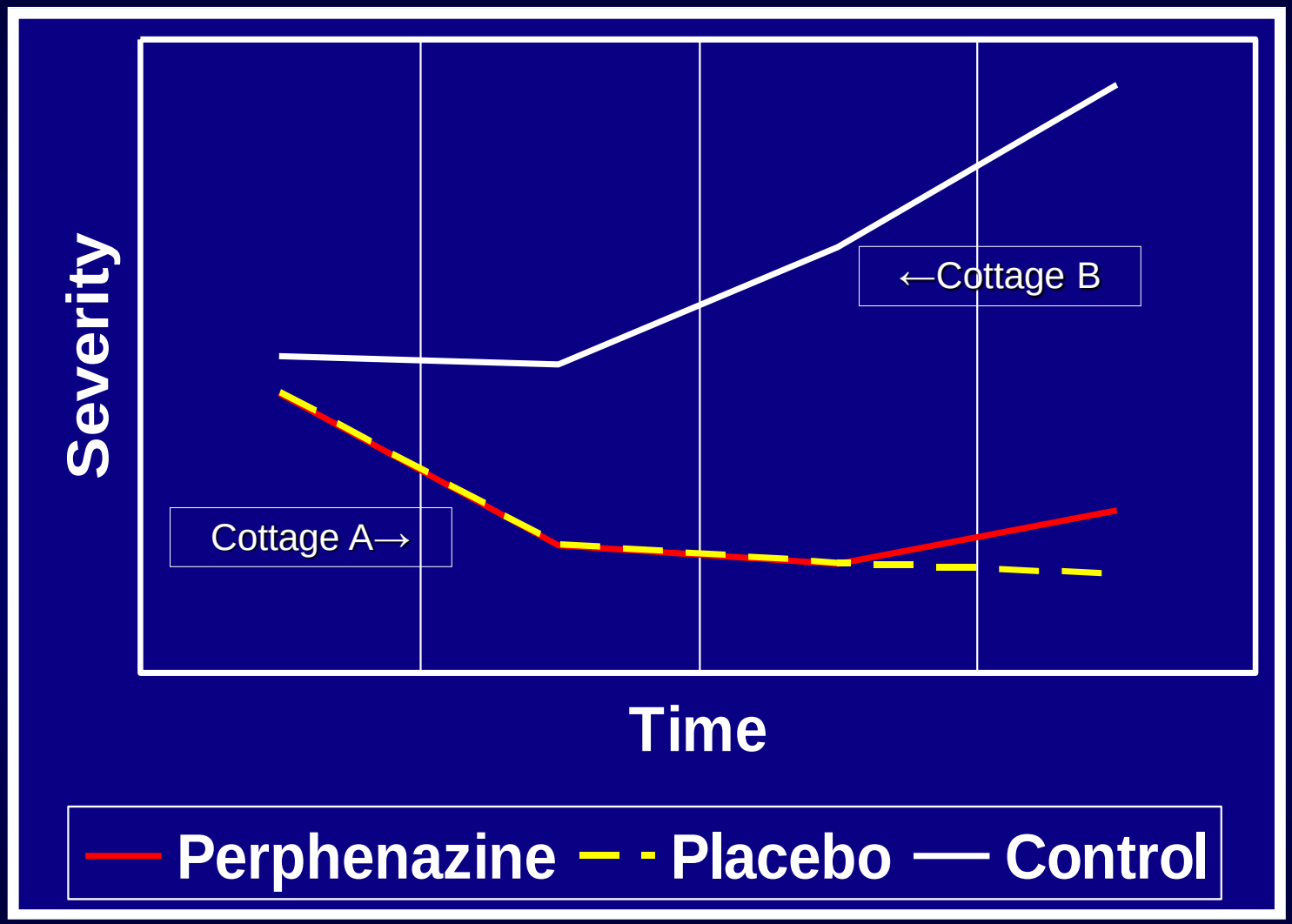

*Sum of 5 items, range 0-15.

Klein RG et al. *Arch Gen Psychiatry.* 1997;54:1073-1080.

# Overview: Psychosocial Approaches for Aggression

- Effective treatments for aggressive youth combine psychosocial and pharmacological interventions
- Outcomes may be optimized when medication is administered as part of a comprehensive treatment program

# Neuroleptics and Placebo Effect



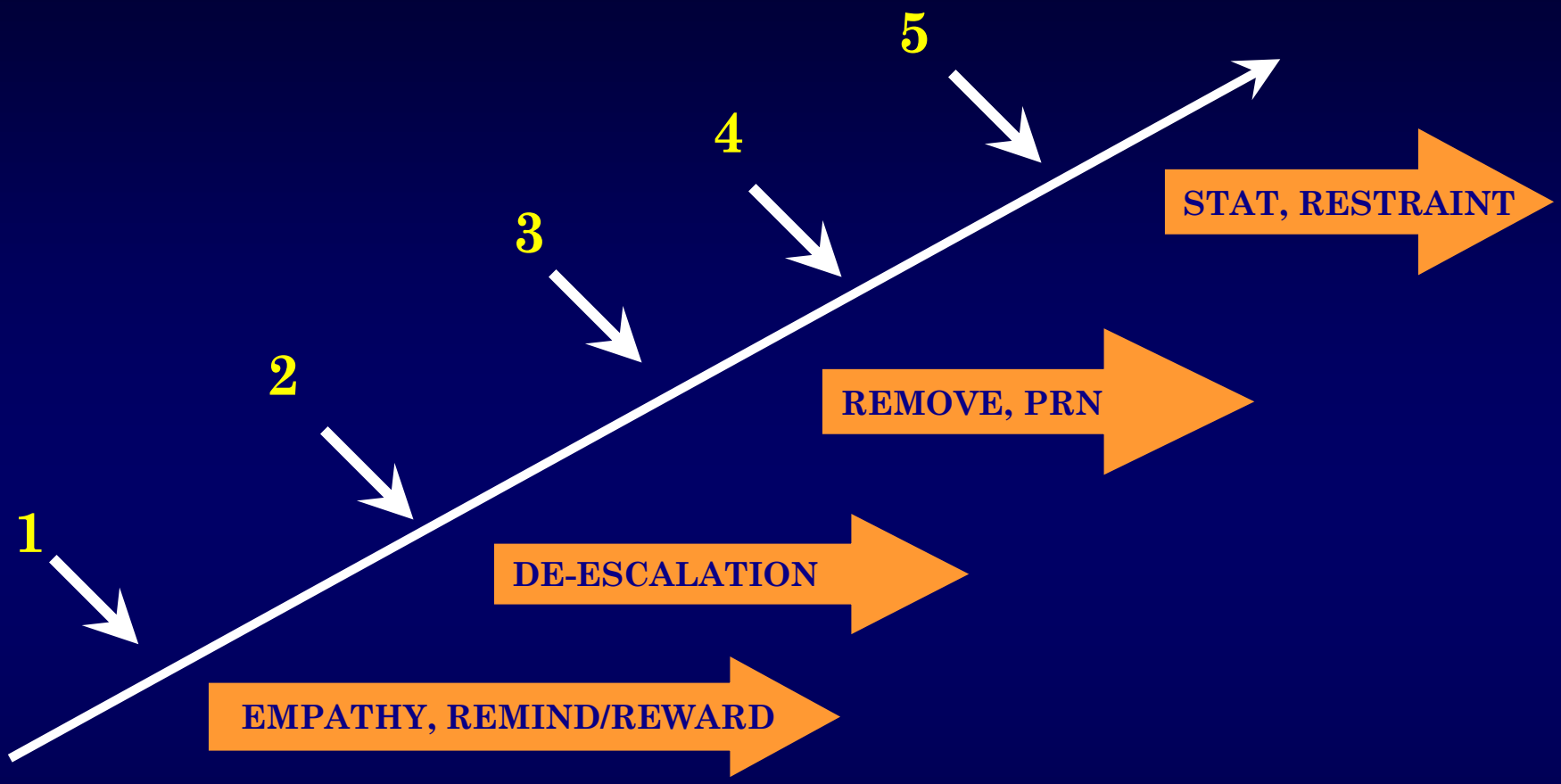

Molling PA, Lockner AW, Sauls RJ, et al (1962). *Arch Gen Psychiatry* 7:96-102.

# Behavioral Programs Can Lead to Reductions in Restraint and PRNs

- A behavioral program was implemented on a coeducational residential unit for six months. It involved the use of:
  - A token economy
  - Exclusionary timeouts (i.e, a timeout room)
  - Response costs or fining
- Emergency mechanical restraints decreased by 79% during program phase and 81% during maintenance phase
- PRNs reduced by 79% during program phase and 75% during maintenance phase

Foxx, RM (1998). *Behav Interventions* 13:67-77.

# Acute Agitation/Aggression




Arrow points:

1 - early warning signs of difficulty
2 - noticeable agitation
3 - inappropriate language or threats of violence
4 - property damage
5 - clear safety risk, aggression toward self or others, unresponsive to other interventions

# Stat/PRN May Be No Better Than Placebo

- n=21, inpatient males (ages 5-13 years)
  - dx.: CD, ADHD, and major depression
- Double-blind placebo-controlled study of the prn use diphenhydramine. Patients in acute dyscontrol received either oral or IM dose of diphenhydramine, 25-50 mg (n=9) or placebo
- CGI completed .5, 1 & 2 hours after dose
- Results: No difference between the two treatments
- IM more effective than PRN

Vitiello B, Hill JL, Elia J, et al (1991). *J Clin Psychiatry* 52(12): 499-501.

# Acute Aggression/Crisis Management

- Use psychosocial crisis-intervention strategies before medication
  - e.g. de-escalation, time outs, etc.
- When behavioral strategies fail to control agitated/aggressive behavior:
  - Employ limited use of STATs or PRN
  - Avoid frequent use of IM or PRN
- Re-evaluate regimen of patient who requires multiple STAT/PRNs

# Emphasis on Continual Improvement

## Treatment Team Review of Restrictive Intervention

- Staff/setting: Identify methods for preventing future emergencies
- Patient: evaluate/revise  treatment/medication plan
- Closely monitor for frequency and type of restrictive interventions used
- Evaluate progress regularly with treatment team

# Pharmacologic Treatment of Impulsive Aggression: When Treatment of The Primary Disorder is not Enough:

- Aggressive symptoms often require simultaneous use of antipsychotics with first-line treatments for primary conditions

- Use an atypical antipsychotic as first-line treatment for aggression
  - If no response, try a second atypical agent
  - If a partial response, consider adding a mood stabilizer

*Atypical antipsychotic therapy in children/adolescents represents off-label prescribing.

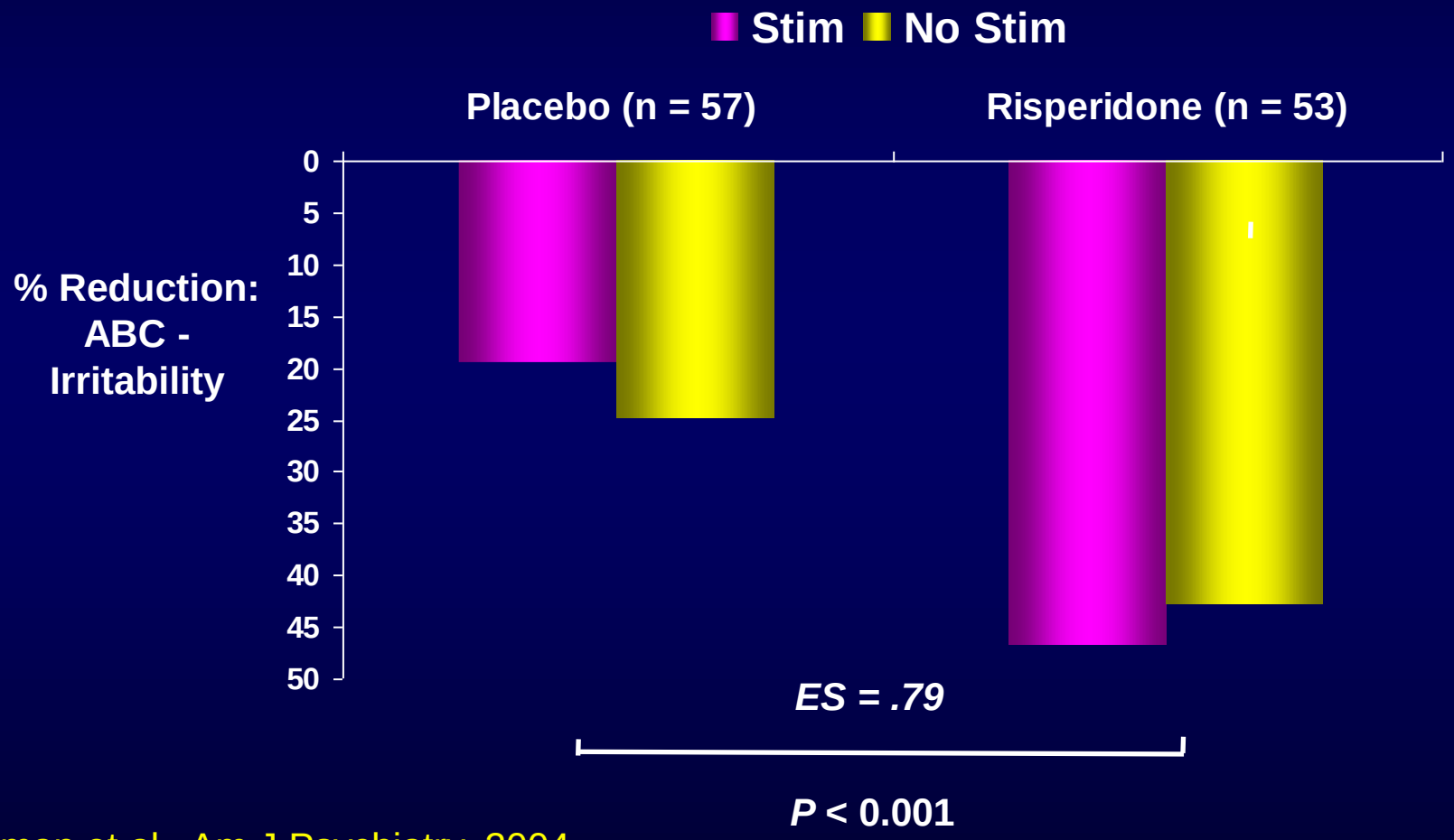
# Pharmacologic Treatment of Impulsive Aggression: When Treatment of The Primary Disorder is not Enough:

- Dosing strategies should
  - Be conservative
    - "Start low, go slow, taper slowly"
  - Minimize use of emergency drug treatment (prn or stat)

- Use atypical antipsychotic agent at adequate dose for appropriate period before making changes

*Atypical antipsychotic therapy in children/adolescents represents off-label prescribing.

# Risperidone in ADHD: Changes in ABC Irritability/Aggression




Aman et al., Am J Psychiatry, 2004.

# Atypical Antipsychotics: Optimal Dosing/Titration Strategies for Children and Adolescents

| Atypical Antipsychotics | Starting Daily-Dose | Titration Dose, q3-4 day (~Min. days to antipsychotic dose) | Usual Daily Dose Range in Aggression** | | Usual Daily Dose Range in Psychosis | |
|---|---|---|---|---|---|---|
| | | | CHILD | ADOLESCENT | CHILD | ADOLESCENT |
| Aripiprazole | 2.5-5 mg | 2.5-5 mg (7-10 days) | 2.5-15 mg | 5-15 mg | 5-15 mg | 5-30 mg |
| Clozapine | 6.25-25 mg | 1-2x starting dose (18-30 days) | 150-300 mg | 200-600 mg | 150-300 mg | 200-600 mg** |
| Olanzapine | 2.5 mg for children 2.5-5 mg for adolescents | 2.5 mg (10-15 days) | NDA | NDA | 7.5-12.5 mg | 12.5-20 mg |
| Quetiapine | 12.5 mg for children 25 mg for adolescents | 25-50 mg to 150 mg then 50-100 mg (18-30 days) | NDA | NDA | NDA | 300-600 mg |
| Risperidone | 0.25 mg for children 0.50 mg for adolescents | 0.5-1 mg (10-15 days) | 1.5-2 mg | 2-4 mg | 3-4 mg | 3-6 mg |
| Ziprasidone | 20 mg | 20 mg for children 20-40 for adolescents (18-30 days) | NDA | NDA | NDA | NDA; (In adults, 160-180 mg) |

NDA = no data available.

*There is little information to guide dosing strategies for aggression. However, for aggressive children treated with risperidone, doses are about half that of the usual antipsychotic dose.

**In treatment resistant schizophrenic adults, a serum clozapine level (of the parent compound) greater than 350mg/dl is generally required for efficacy.

# AP Side Effects
# Broad Continuum of Severity