

Bipolar Disorder vs. Chronic Irritability in Children: Diagnosis and Treatment

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Talk Outline

- **Diagnosing bipolar disorder (vs. chronic, severe irritability)**
 - **The importance of episodes**
- **Treatment of pediatric bipolar disorder**
- **Treatment of irritability in youth**

Increase in diagnosis of BD in youth

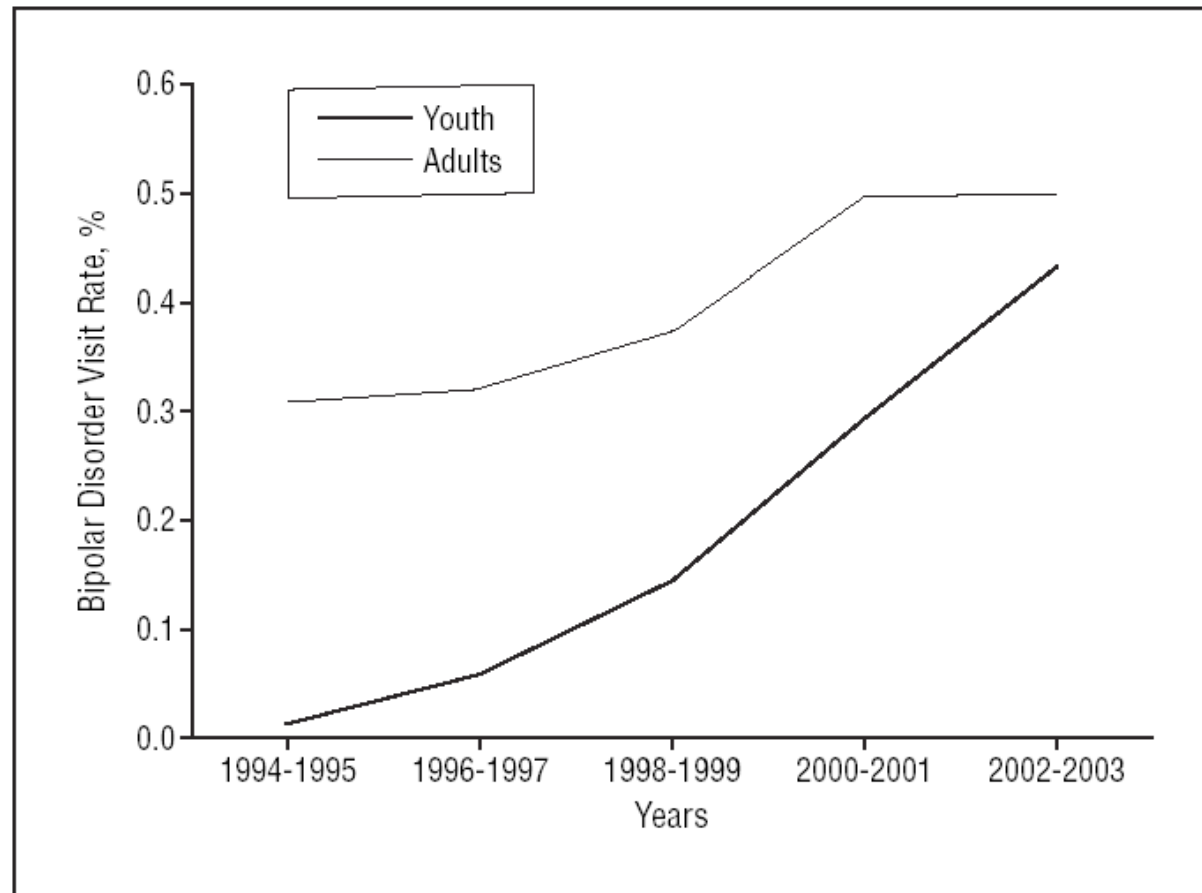


Figure. National trends in visits with a diagnosis of bipolar disorder as a percentage of total office-based visits by youth (aged 0-19 years) and adults (aged ≥ 20 years).

Hospital discharge diagnoses in the U.S., 1996-2004

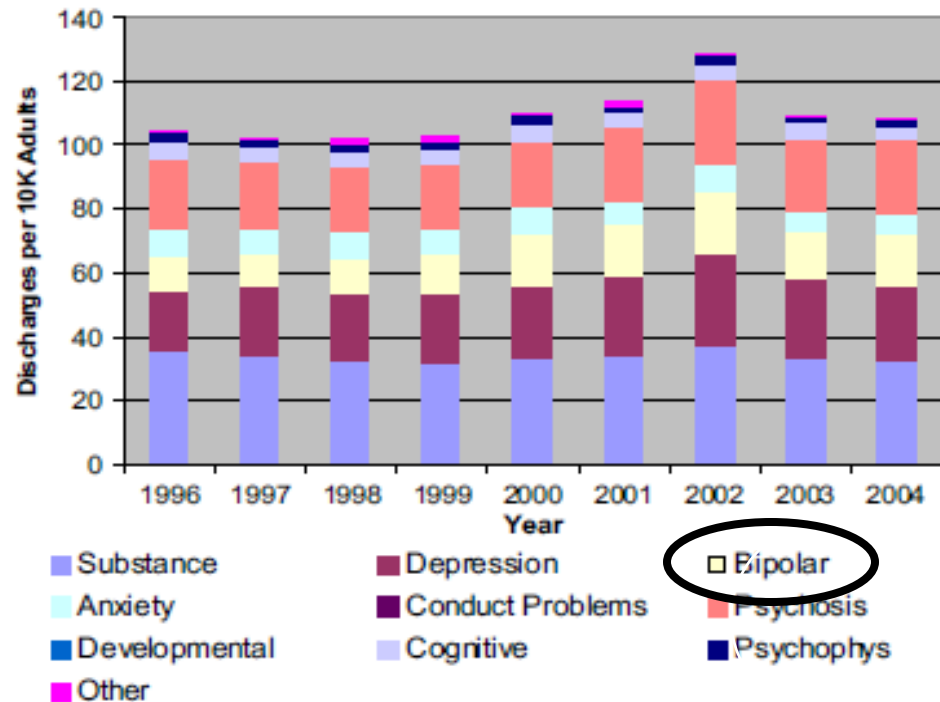
Rate of increase in d/c's for BD:

In adults, 56%

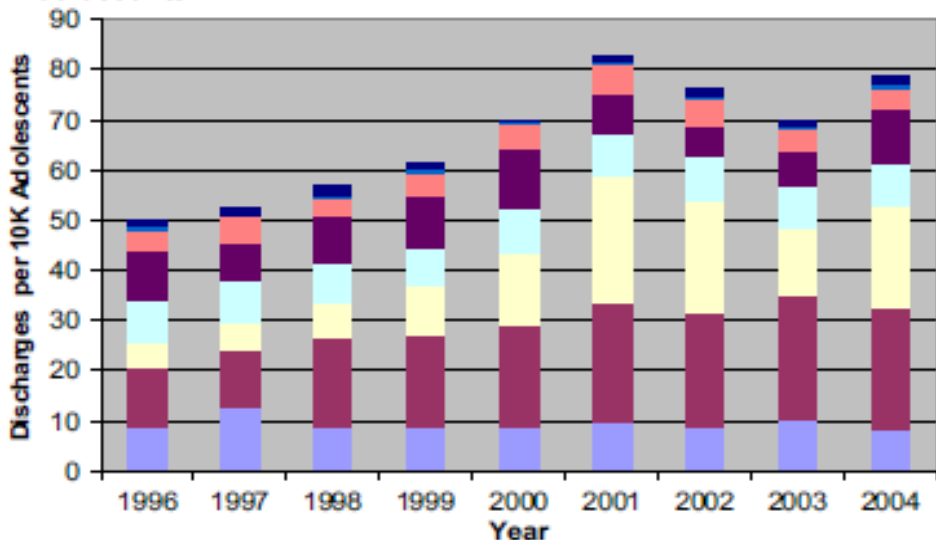
In adolescents, 400%

In children, 1.3 to 7.3 per 10,000 (~600%)

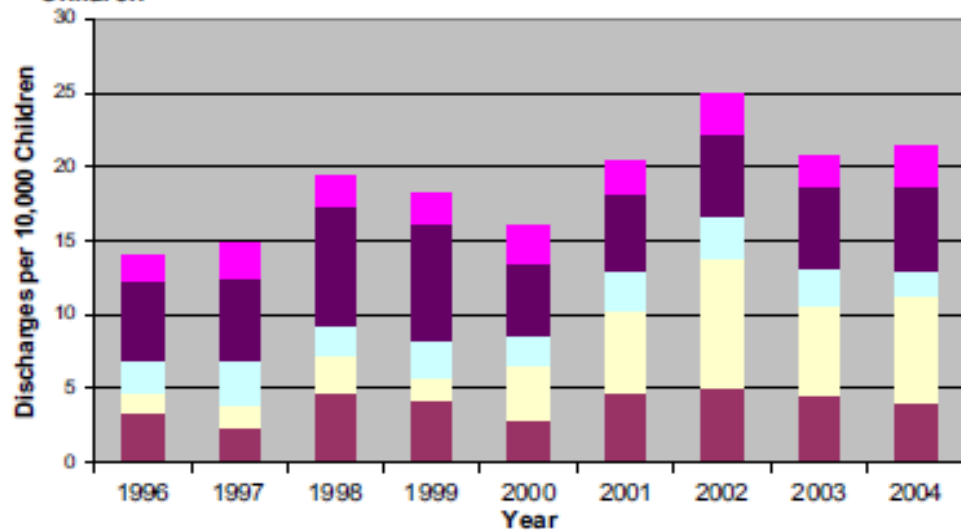
Adults



Adolescents



Children



Diagnosing pediatric bipolar disorder: The controversy in the US

**Is severe irritability and ADHD,
without distinct manic episodes,
a developmental form of bipolar disorder?**

DSM-IV Criteria for Manic Episode: Unique features

- A. **Distinct period** of **elevated, expansive**, or irritable mood \geq 1 week

- B. Symptoms (3, or 4 if irritable) **at the same time as "A"**
 - (1) **grandiosity**
 - (2) **decreased need for sleep**
 - (3) pressured speech
 - (4) flight of ideas, racing thoughts
 - (5) distractibility
 - (6) **increased goal-directed activity**, psychomotor agitation
 - (7) excessive pleasurable activities

- C. Marked impairment, hospitalization, or psychosis

DSM-IV Criteria for Manic Episode: **Overlap with ADHD**

A. Distinct period of elevated, expansive, or **irritable** mood present most of the day, nearly every day \geq 1 week

B. Symptoms (3 of the following, or 4 if mood only irritable) occur at the same time as "A"

(1) inflated self-esteem, grandiosity

(2) decreased need for sleep

(3) pressured speech

(4) flight of ideas, racing thoughts

(5) distractibility

(6) increased goal-directed activity, psychomotor agitation

(7) excessive, pleasurable activities with potential for painful consequences

ADHD-like
symptoms



C. Marked impairment, hospitalization, or psychotic features

DSM-5 Criteria for Manic Episode: Differences from DSM-IV

- A. Distinct period of elevated, expansive, or irritable mood and **abnormally and persistently increased goal-directed activity or energy lasting at least one week and present most of the day, nearly every day \geq 1 week**
- B. Symptoms (3, or 4 if irritable) occur at the same time as “A” **and represent a noticeable change from previous behavior:**
- (1) grandiosity
 - (2) decreased need for sleep
 - (3) pressured speech
 - (4) flight of ideas, racing thoughts
 - (5) distractibility
 - (6) increased goal-directed activity, psychomotor agitation
 - (7) excessive pleasurable activities

Bottom line

According to the DSM, you should diagnose bipolar disorder **ONLY** if there is a history of a **distinct manic or hypomanic episode**

Diagnosing bipolar disorder in children: Interview tips

- Each child is her/his own baseline.
 - **The child's behavior during the episode must differ from the child's usual behavior.**
- Direct observation has the greatest weight
- **Elevated mood, grandiosity** are the trickiest
 - E.g. What is grandiosity in a 5, 10, 15, 25, 35 year old?
 - **Again, each child is his/her own baseline.**
- **Ascertain episodes:** worst mania, worst depression, euthymia
- ADHD etc. are diagnosed based on symptoms during euthymia.

Does mania occur in preschoolers?

- Commonly reported symptoms include:
 - Irritability
 - Racing thoughts
 - Increased activity
 - Grandiosity
- Problems
 - What is normative?
 - Episodes not described e.g., Luby et al, 2006; Danielyan et al, 2007
- AACAP guidelines advise against assigning dx to preschoolers

Is the DSM wrong?

**Is severe irritability and ADHD,
without distinct manic episodes,
a developmental form of bipolar disorder?**

Research to address the controversy

- One can identify youth (including prepubertal youth) who meet “classic” (DSM-IV) criteria for BD.
- To demonstrate that an alternative phenotype is a developmental presentation of mania, recruit such children and compare them to those with the classic presentation

Severe Mood Dysregulation (SMD)

- Chronic presentation (vs. episodes of BD)
- Irritability clearly defined, with high bar:
 - **baseline anger or sadness**
 - **↑ reactivity to negative emotional stimuli $\geq 3x/week$**
- Irritability impairing in ≥ 2 settings (home, school, peers)
 - **SMD children should be as impaired as BD**
- ADHD symptoms that overlap with “B” mania criteria
- **SMD = DSM-IV: most severely impaired ADHD + ODD**
 - **new diagnosis in DSM-5: Disruptive mood dysregulation disorder (DMDD)**

How does DSM-5 Disruptive Mood Dysregulation Disorder (DMDD) differ from SMD?

- No hyperarousal symptoms (just dx ADHD)
- Can be diagnosed at age 6 (vs. 7)
- Symptoms must begin before age 10 (vs. 12)
- DMDD trumps ODD

Clinical characteristics	BD (N=131)	SMD (N=201)
Age	13.1 ± 2.8	11.7 ± 4.4
Age of onset	10.1 ± 3.3	5.1 ± 2.4
Gender (% male)	53.4	65.2
% ADHD	57.2	86.1
% ODD	37.1	83.6
% Anxiety d/o	74.4	66.7
Number meds	2.4 ± 1.7	2.1 ± 1.5
Children's Global Assessment Scale	50.1 ± 11.3	47.0 ± 8.0

Is SMD a developmental form of bipolar disorder?

Longitudinal Outcome and Family History

Over time, do youth with severe irritability develop manic episodes?

Is there a familial association between severe irritability and BD?

categorical (DSM) vs. dimensional (RDoC) perspective

Why does it matter whether SMD is a form of BD?

- **Treatment!!!**
- **If SMD = BD, then antipsychotic medication, anticonvulsants**
 - **Stimulants and SRI's relatively contraindicated**
- **If SMD = ADHD + anxiety and/or depression, then stimulants and SRI's (ongoing trial)**

Longitudinal Outcome

An important positive outcome of the controversy about the diagnosis of pediatric bipolar disorder

- **Highlights that irritability is a common, yet relatively understudied, clinical presentation in children**
- **Regarding irritability, we need to know much more about:**
 - clinical correlates
 - outcomes
 - **treatment**
 - measurement
 - pathophysiology and pathogenesis
 - impact of genes, environment, G X E interactions and correlations
 - neural circuitry

**Do children with severe irritability develop BD
when they grow up?**

Community-based studies:

**Irritability in youth predicts anxiety,
unipolar depression in adulthood, not
bipolar disorder**

Chronic irritability in youth predicts MDD, dysthymia, anxiety at f/u

	N	Age at baseline	Age at f/u	MDD	GAD	Dysth	MDD & GAD
Children in the Community	776	13.8	33.2	1.33 (1.0-1.8)	1.72 (1.0-2.9)	1.81 (1.1-3.1)	n/a

Chronic irritability did not predict mania or Axis II Disorders.

Stringaris et al, 2009

Three strands of research on irritability in youth

- From pediatric bipolar disorder to severe mood dysregulation
- Increased interest in emotional dysregulation in youth with ADHD
 - Martel, 2010; Sobanski et al, 2010; Hamshere et al, 2013; Spencer et al, 2011
- Oppositional defiant disorder (ODD) has two dimensions
 - Headstrong predicts to conduct disorder
 - **Irritable dimension of ODD predicts to unipolar depressive and anxiety disorders**
 - Stringaris and Goodman 2009, Rowe et al 2010, Burke et al, 2010

Dimensions of oppositionality and their association with diagnoses

Two community-based samples (N=7,912)
3-year follow-up (10.2 ± 3.3 y to 13.2 ± 3.3 y)

Irritable

had temper outbursts?
been touchy or easily annoyed?
been angry and resentful?

Headstrong

argued with grown-ups?
taken no notice of rules, or refused to do as she/he is told?
seemed to do things to annoy other people on purpose?
blamed others for his/her own mistakes or bad behavior?

	Internalizing Disorders	ADHD	Conduct Disorder
Irritable			
Unadjusted	2.33*** (1.63–3.34)	1.4 (0.93–2.17)	1.16 (0.79–1.73)
Adjust for baseline diagnoses	1.77*** (1.21–2.57)	1.13 (0.69–1.85)	1.04 (0.69–1.58)
Adjusted for baseline score	1.54*** (1.05–2.27)	1.25 (0.81–1.93)	1.12 (0.74–1.71)
Headstrong			
Unadjusted	0.90 (0.61–1.32)	3.27*** (2.08–5.11)	2.54*** (1.68–3.84)
Adjust for baseline diagnoses	0.93 (0.62–1.39)	1.89*** (1.13–3.14)	2.12*** (1.38–3.26)
Adjusted for baseline score	0.95 (0.64–1.42)	2.15*** (1.35–3.41)	1.60*** (1.02–2.51)

Do children with severe irritability develop BD when they grow up?

Community-based studies:

- Irritability in youth predicts anxiety, unipolar depression in adulthood, not bipolar disorder

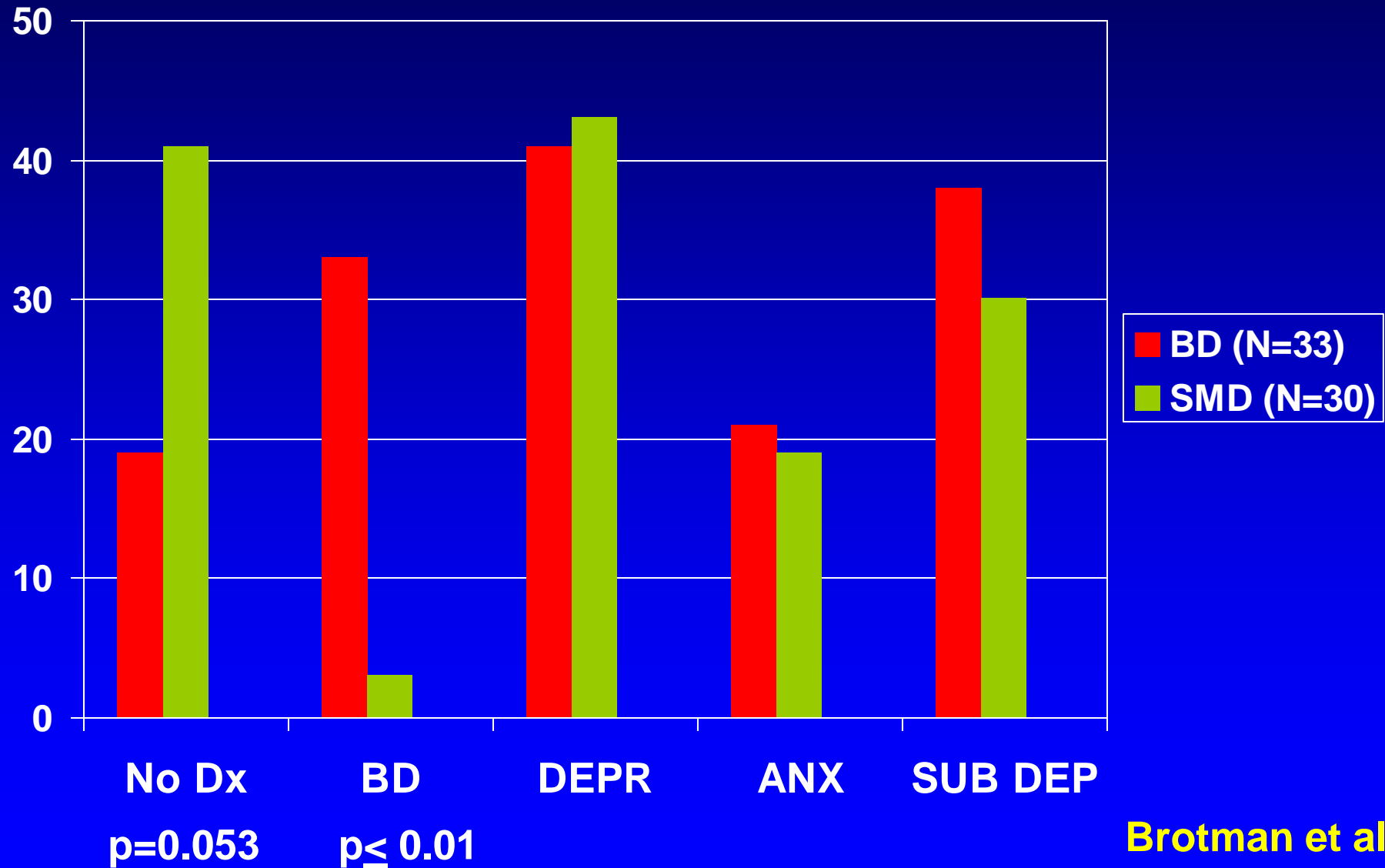
NIMH study of patients:

- 3/200 SMD children followed for ≤ 4 years developed a manic episode

But...we don't know about the special case of children with a parent with bipolar disorder

Family History

Psychiatric illness in parents of youth with BD or SMD



Longitudinal Assessment of Manic Symptoms (LAMS)

- Screened 2622 youth presenting for assessment
- 25% (N=235) met proxy criteria for DMDD
- Compared DMDD vs. non-DMDD in
 - rates of BD in 1st degree relatives
 - Rates of BD in 1st and 2nd degree relatives
 - Degree of familial loading for mania (% family members assessed who met criteria)
- No analysis reached significance, even before correcting for multiple comparisons

D Axelson, RL Findling, EA Youngstrom, MA Fristad, B Birmaher, RA Kowatch, LE Arnold, TW Frazier, N Ryan, CA Demeter, MR Gill, B Fields, J Depew, SM Kennedy, L Marsh, BM Rowles, SM Horowitz (unpublished)

Treatment of pediatric bipolar disorder

FDA-approved medications for pediatric mania

Lithium for children ≥ 12

Risperidone for children ≥ 10

Aripiprazole for children ≥ 10

Quetiapine for children ≥ 10

Olanzapine for youth $\geq 13^*$

*Labeling: consider other medications first

Goldstein, Sassi, Diler: Pharmacologic treatment of bipolar disorder in children and adolescents. Child and Adolescent Psychiatric Clinics of North America 21: 911, 2012

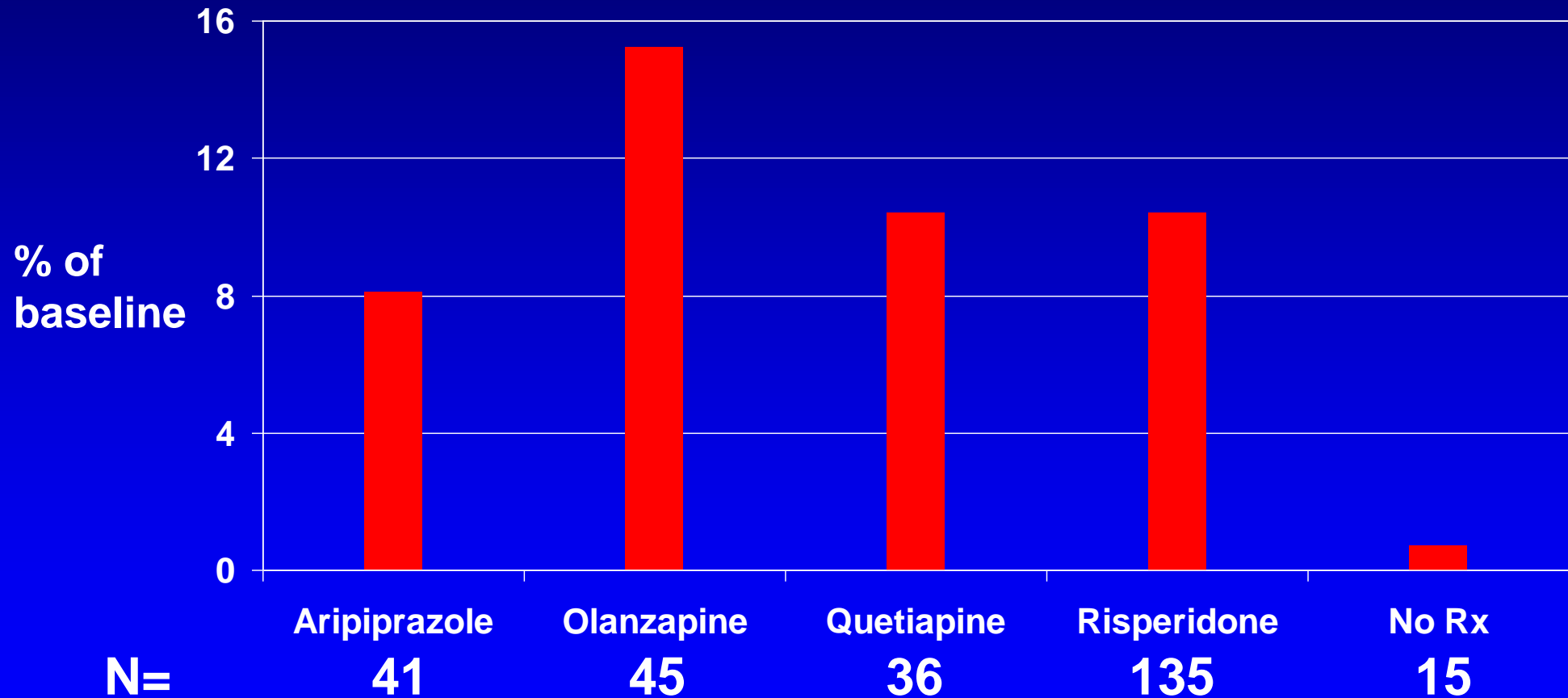
Comparing mood stabilizers and 2nd generation antipsychotics: Efficacy

Outcome	Children and adolescents				SGA versus MS in youth
	SGA trials (n = 1,118)		MS trials (n = 494)		
Continuous outcome	ES^a	95% CI^a	ES	95% CI	
YMRS ^a	0.65	0.53–0.78	0.24	0.06–0.41	SGA > MS
YMRS ^b			0.20	0.02–0.39	SGA > MS
CGI-BP overall illness ^a	0.63	0.50–0.76	0.47 ^c	–	N/A
CGI-BP overall illness ^b			0.47 ^c	–	N/A
Categorical outcome	NNT^a	95% CI^a	NNT	95% CI	
Response: ≥ 50% ↓YMRS ^a	4.0	3.3–5.3	7.8^c	4.7–24.4	NS
Response: ≥ 50% ↓YMRS ^b			7.8^c	4.7–24.4	NS
Remission: YMRS ≤ 12 ^a	3.7	3.1–4.7	–33.3 ^c	–6.8–10.0 ^d	NS
Remission: YMRS ≤ 12 ^b			–33.3 ^c	–6.8–10.0 ^d	NS
All cause discontinuation ^a	12.7	7.5–41.2	–100.0	–8.0–6.3 ^d	NS
All cause discontinuation ^b			15.6	–7.9–4.3 ^d	NS
Discontinuation due to inefficacy ^a	12.5	7.8–31.9	13.3	–32.4–5.5 ^d	NS
Discontinuation due to inefficacy ^b			6.9	3.5–89.6	NS

Comparing mood stabilizers and 2nd generation antipsychotics: Side-effects

Outcome	Children and adolescents				SGA versus MS in youth
	SGA trials (n = 1,118)		MS trials (n ^a = 494; n ^b = 438)		
Continuous outcome	ES	95% CI	ES	95% CI	
Weight change	0.53	0.41–0.66	0.10 ^{a,d}	-0.12–0.33	SGA > MS
			0.48 ^b	0.24–0.72	NS
Categorical outcome	NNH	95% CI	NNH	95% CI	
> 70% weight gain	10.0	7.5–14.0	–	–	–
Somnolence	4.7	3.9–6.0	9.5	6.3–23.5	SGA > MS
Insomnia	100.0 ^c	-47.1–24.0	15.1 ^c	-15.3–5.0	NS
Extrapyramidal side effects	7.5	5.7–11.0	–	–	–
Akathisia	20.4	14.1–36.5	–	–	–
Hyperprolactinemia	7.9	6.1–11.1	–	–	–
Discontinuation due to intolerability	20.4	13.4–47.5	9.2	5.4–36.9	NS

Weight gain during first 11 weeks of Rx



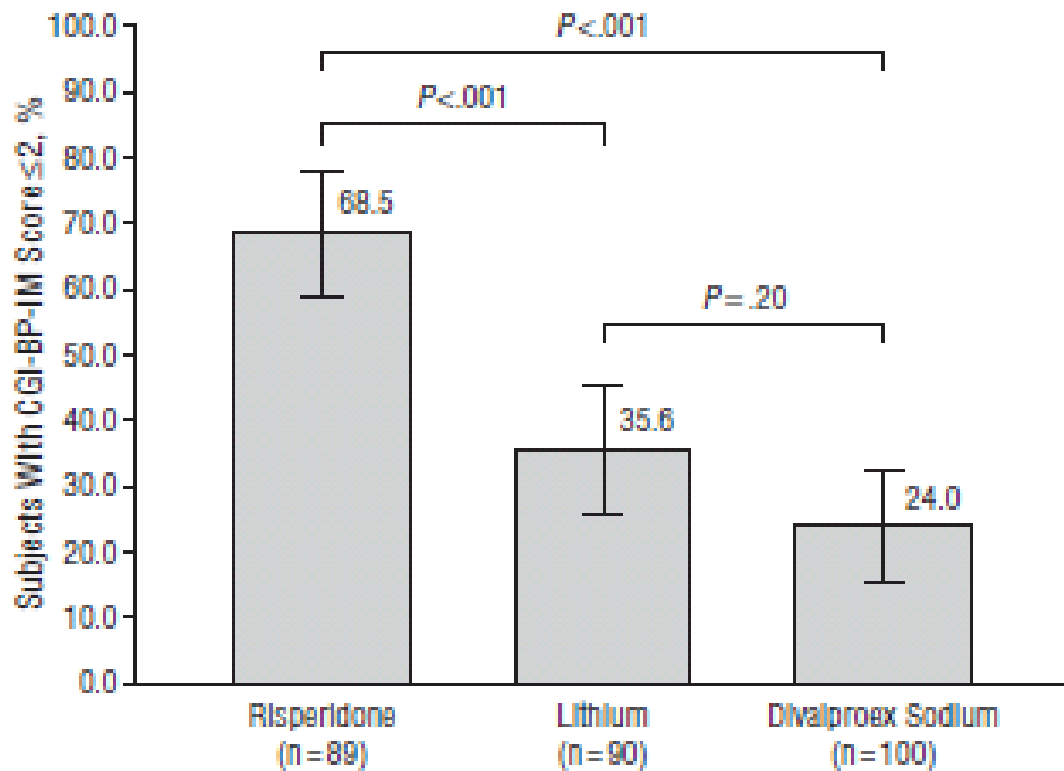
Mean age: 13.9 ± 3.6

Correll et al, 2009

Treatment of Early Age Mania Study

- N=279
- Mean age= 10.1 \pm 2.8y, 50% female
- 8 weeks of treatment
- Randomized to
 - lithium (mean level= 1.09 mEq/L) vs.
 - divalproex sodium (mean level= 113.6 μ g/mL) vs.
 - risperidone (mean dose= 2.57 mg/day)

Clinical Global Improvement for Mania Scores at endpoint



Compared to other treatments, risperidone caused increased:

- weight gain
- BMI
- prolactin

Clinical Characteristics

- **Mania characteristics**

- Mean age mania onset: 5.2 ± 2.6 y
- Mean mania episode duration: 4.9 ± 2.5 y
- # lifetime manic episodes: 1.01 ± 0.08
- Mixed mania: 97.5%
- Daily rapid cycling: 99.3%

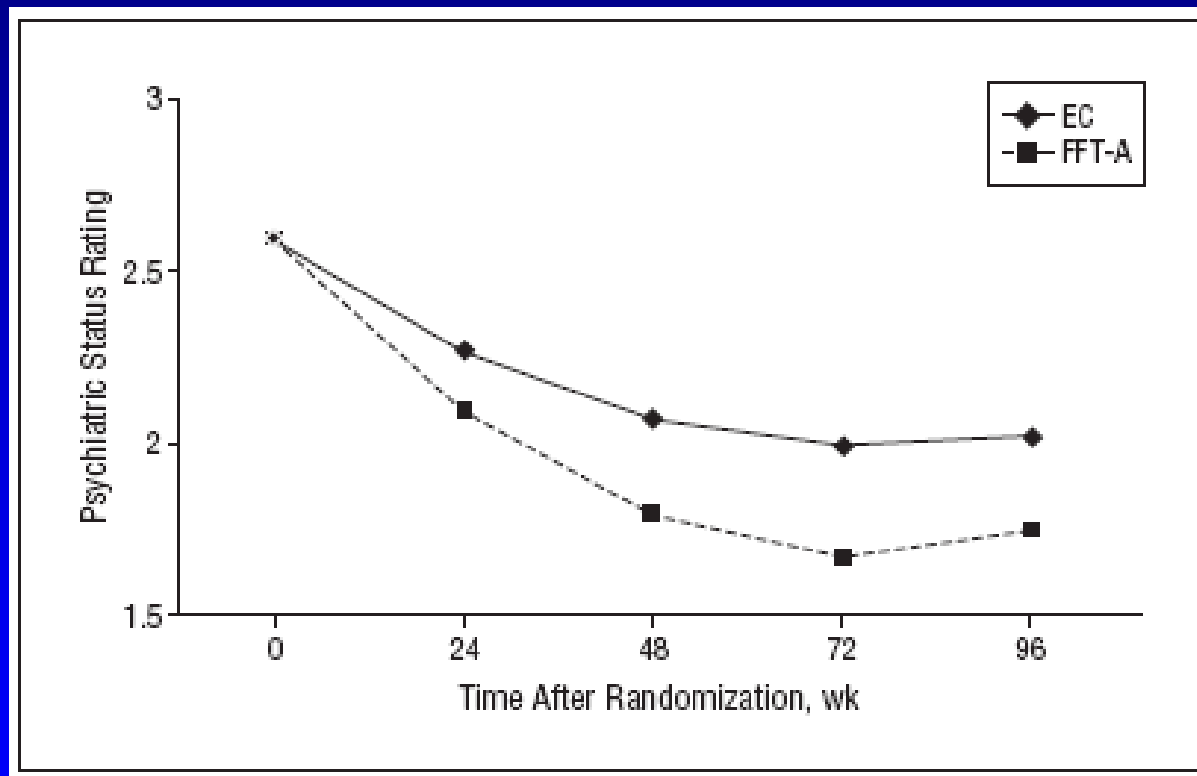
- **Comorbid illnesses**

- ADHD: 92.8%
 - 32.3% receiving stimulant monotherapy at enrollment
- ODD: 90.0%
- Anxiety disorders: 71.3%

Adjunctive family-focused treatment for adolescents with bipolar disorder

21 sessions in 9 months

psychoeducation, communication and problem solving skills training



N=58

Miklowitz et al,
2008

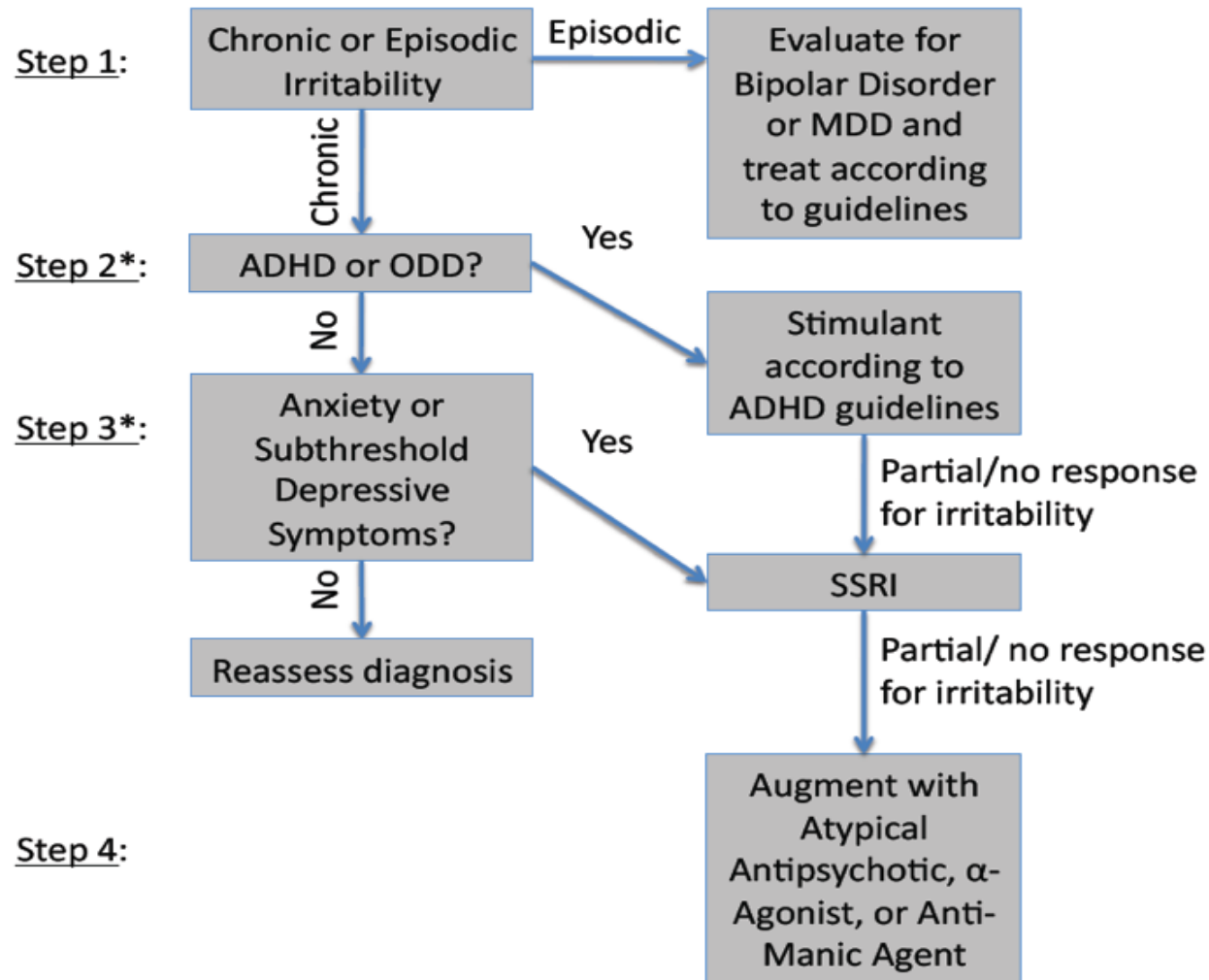
No difference in time to recovery from index episode or to recurrence
Faster recovery from depression, less depression over 2 years

Treatment of severe irritability

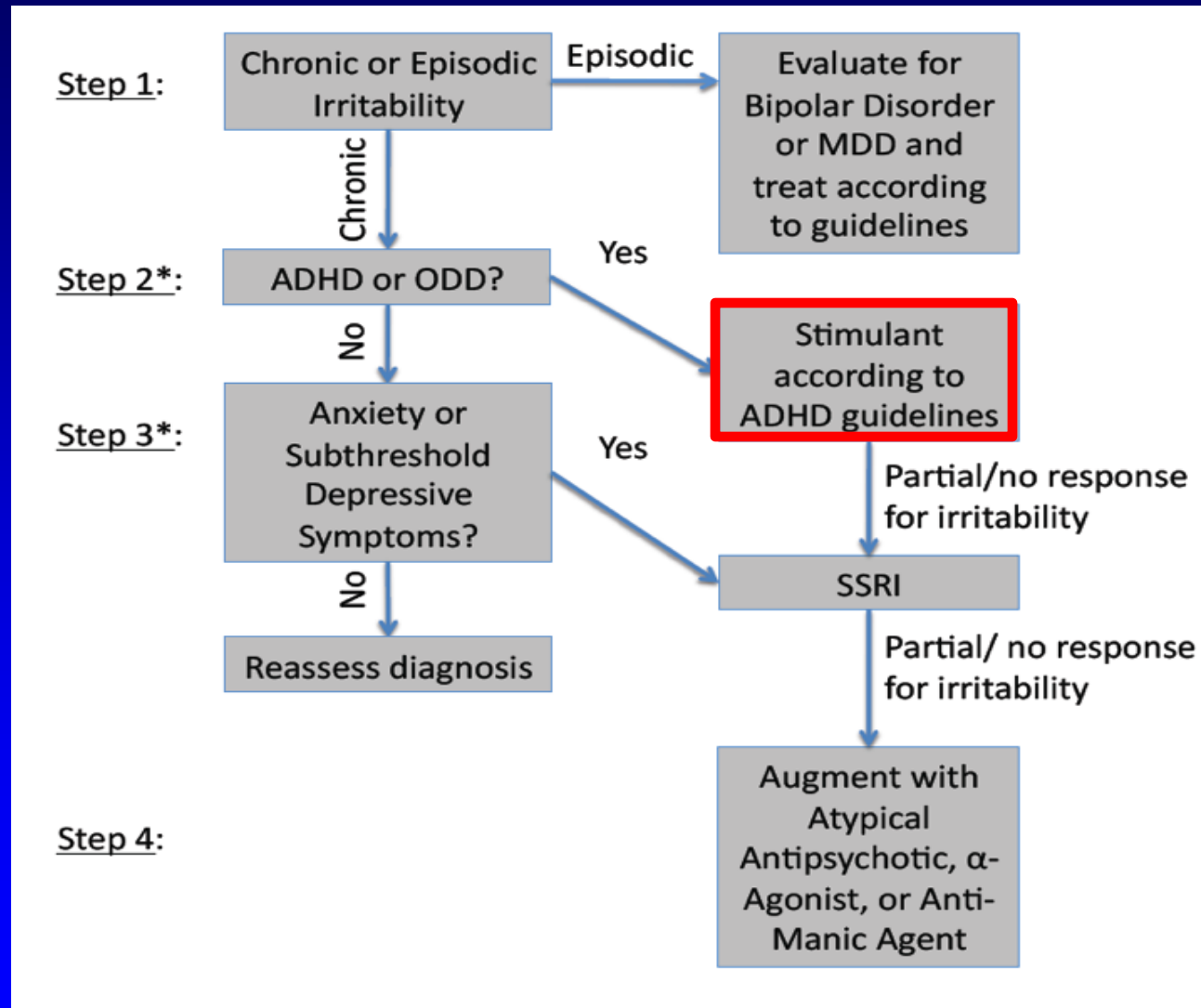
Irritability in DSM-5 Childhood-Onset Disorders

- **Major depressive episode (youth only)**
- **Manic episode**
- **Dysthymic disorder**
- **Post-traumatic stress disorder**
- **Oppositional defiant disorder**
- **Generalized anxiety disorder**

Irritability Treatment Algorithm



Irritability Treatment Algorithm

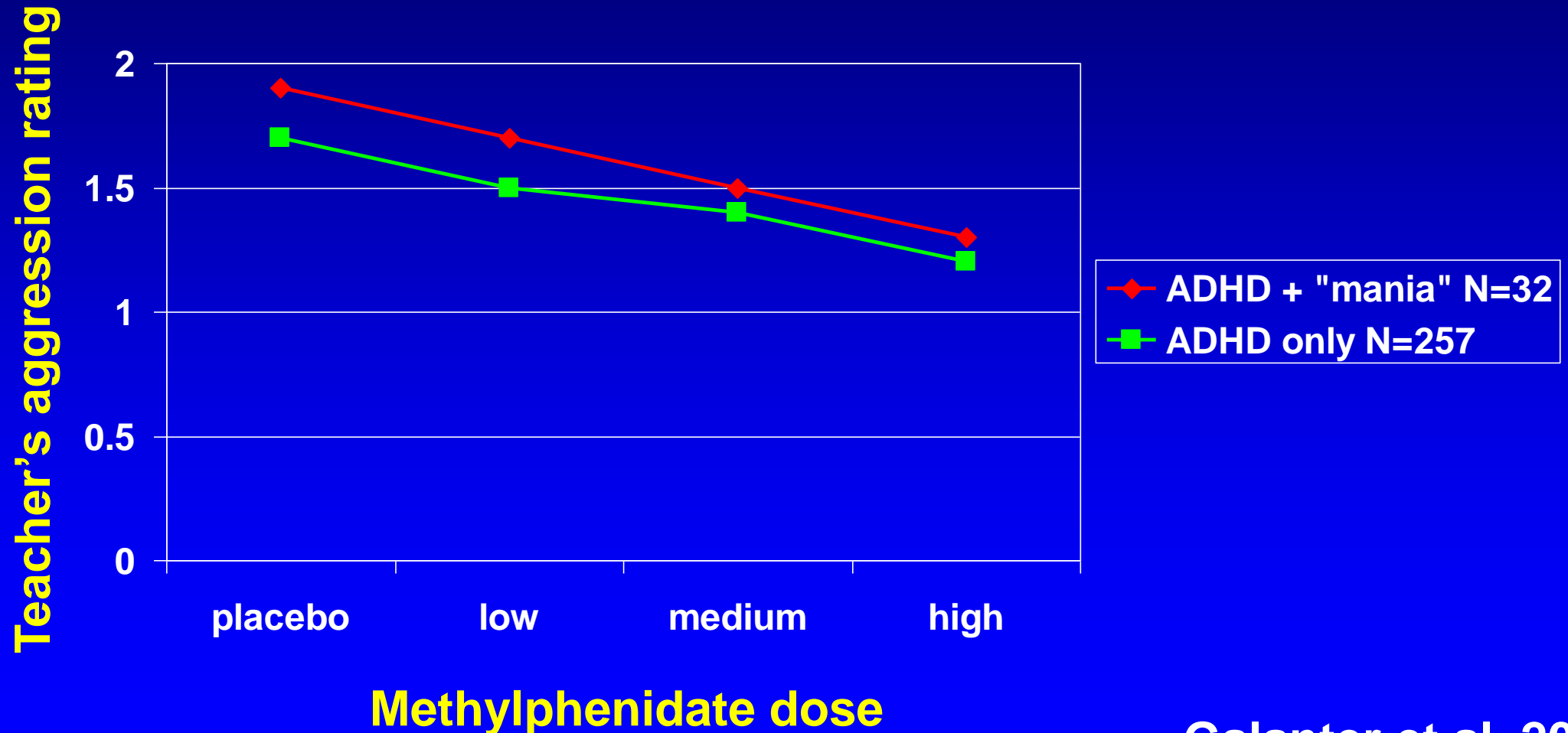


Meta-analysis of efficacy of stimulant Rx on overt and covert aggression

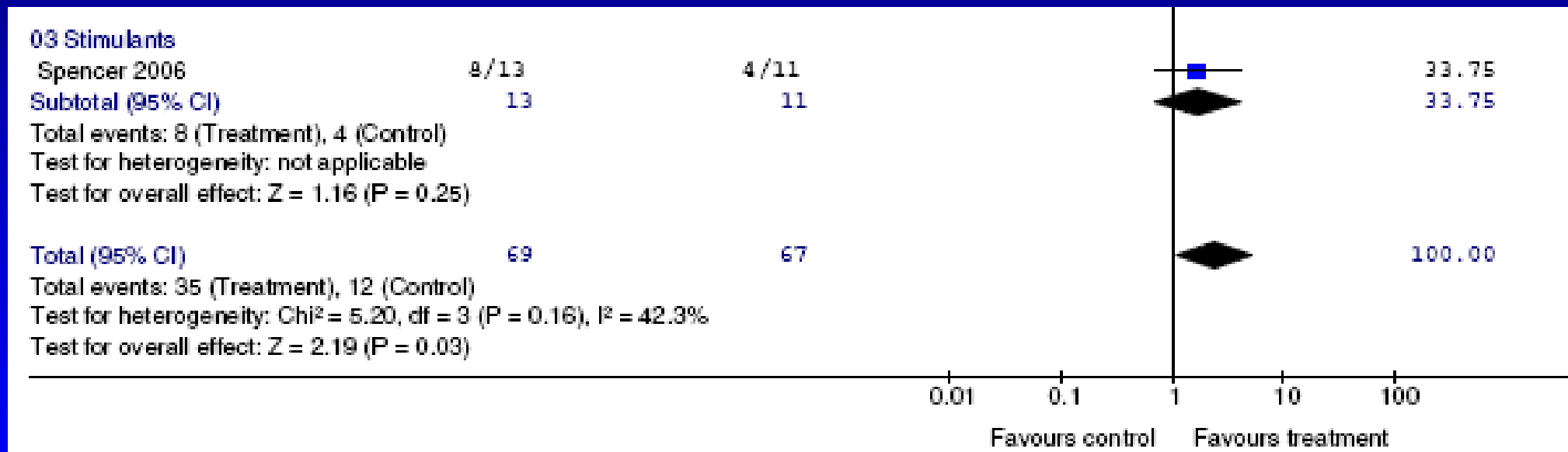
- Included 28 studies, total N=638
- Effect size (Cohen's d)
 - d= 0.84 for overt aggression (included rage attacks, irritability)
 - d= 0.69 for covert aggression

Connor et al, 2002

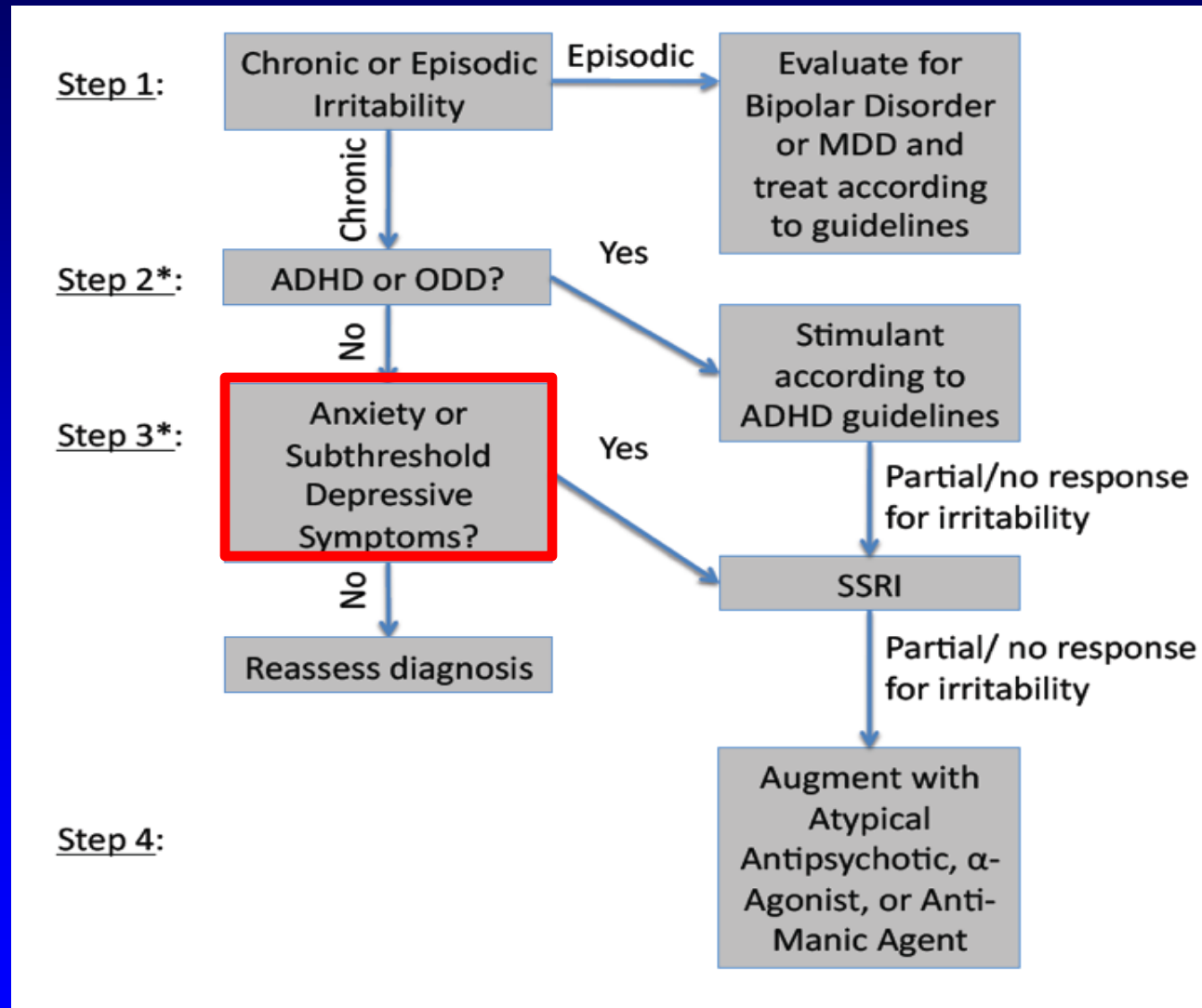
Response to methylphenidate in children with ADHD and manic sx's vs. ADHD alone



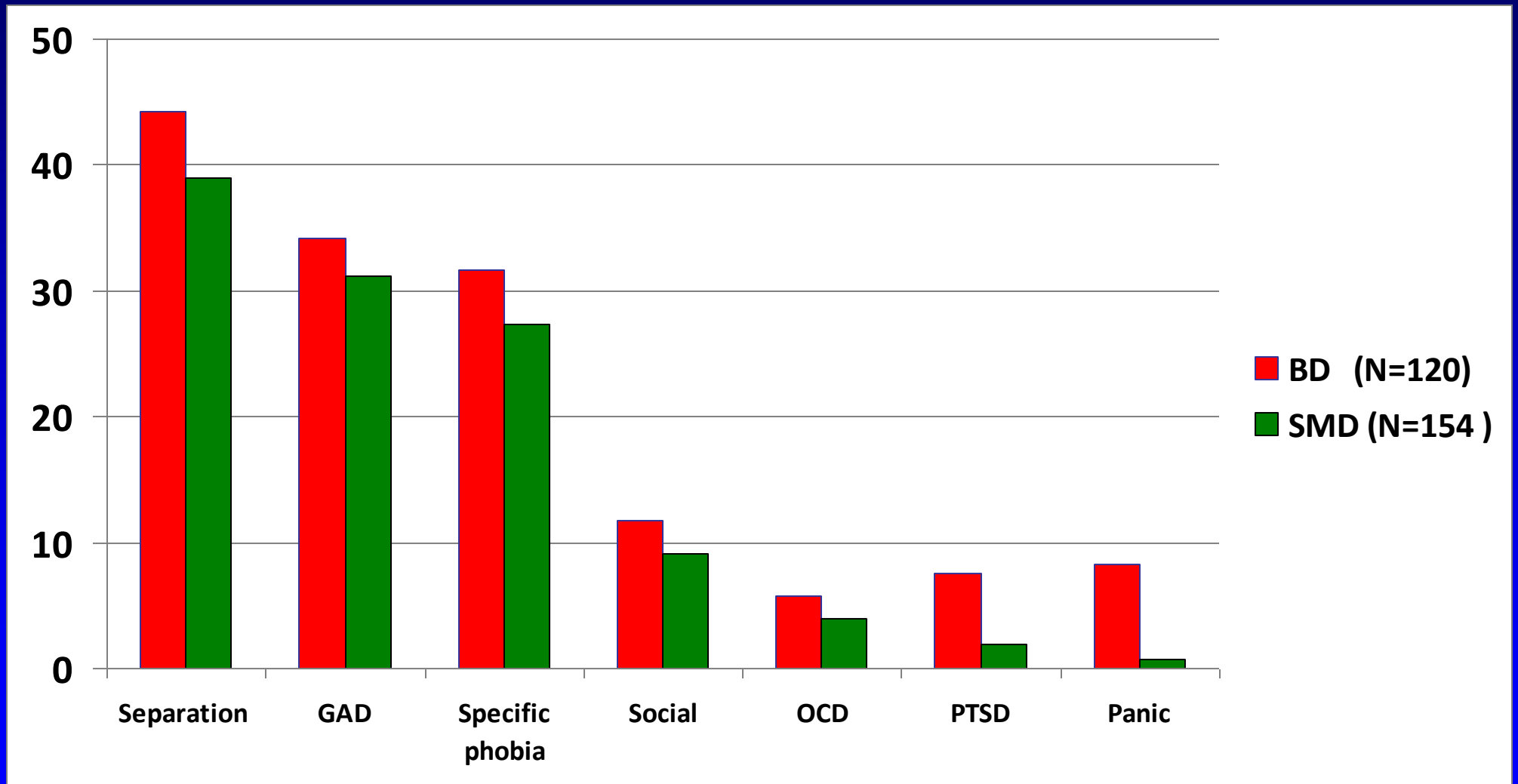
Stimulant treatment for disruptive behavior disorders in youth



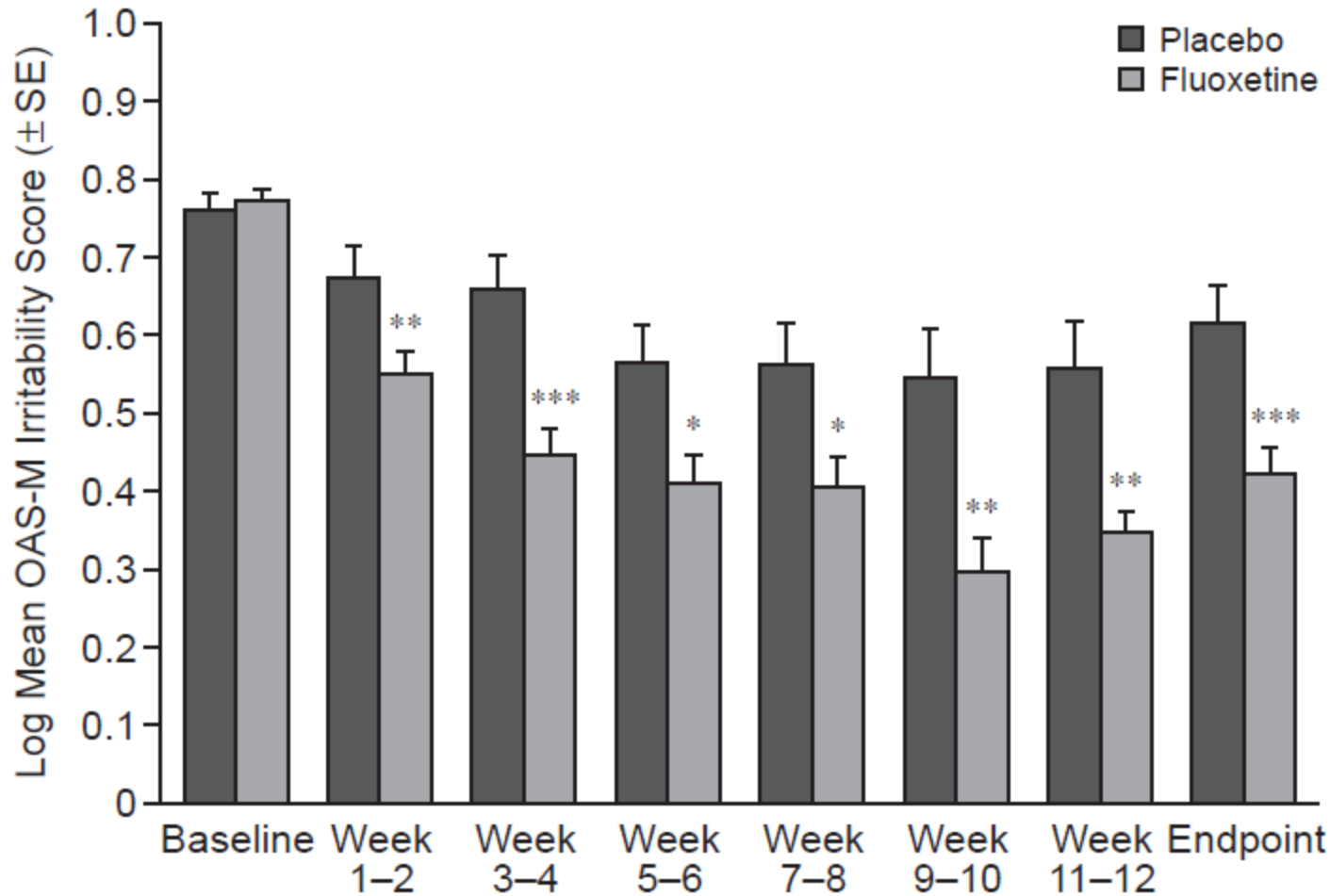
Irritability Treatment Algorithm



Anxiety diagnoses (%) in BD and SMD



Fluoxetine Rx of adults with IED



N=65 FLX, 35 PL
77% male
Age: 36.8 ± 8.7 y
58% hx mood d/o

12 weeks Rx
20-60 mg/d

Fluvoxamine-induced activation

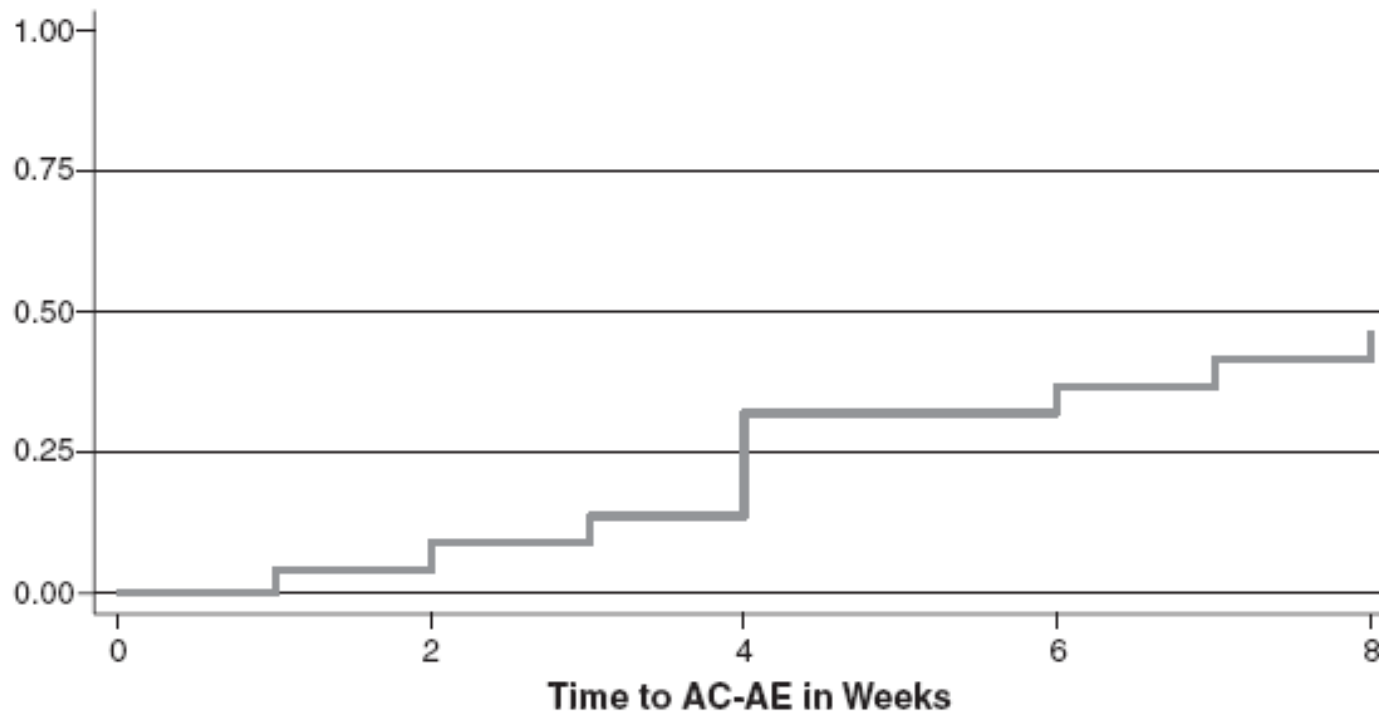


FIG. 2. The Kaplan-Meier estimate of the incidence of AC-AEs by week of fluvoxamine treatment. AC-AEs = Activation cluster-adverse events.

1. Activation: Activated, disruptive, activation, animated;
2. Disinhibition: Disinhibited, doing things they wouldn't normally do, disinhibition, aggression or outburst;
3. Hyperactivity: Hyper, hyperactivity, increased energy.

N=22

Reinblatt et al, 2009

SSRI-associated activation vs. manic switching

- **Activation:** “too much of the same old child”
 - Increased activity level

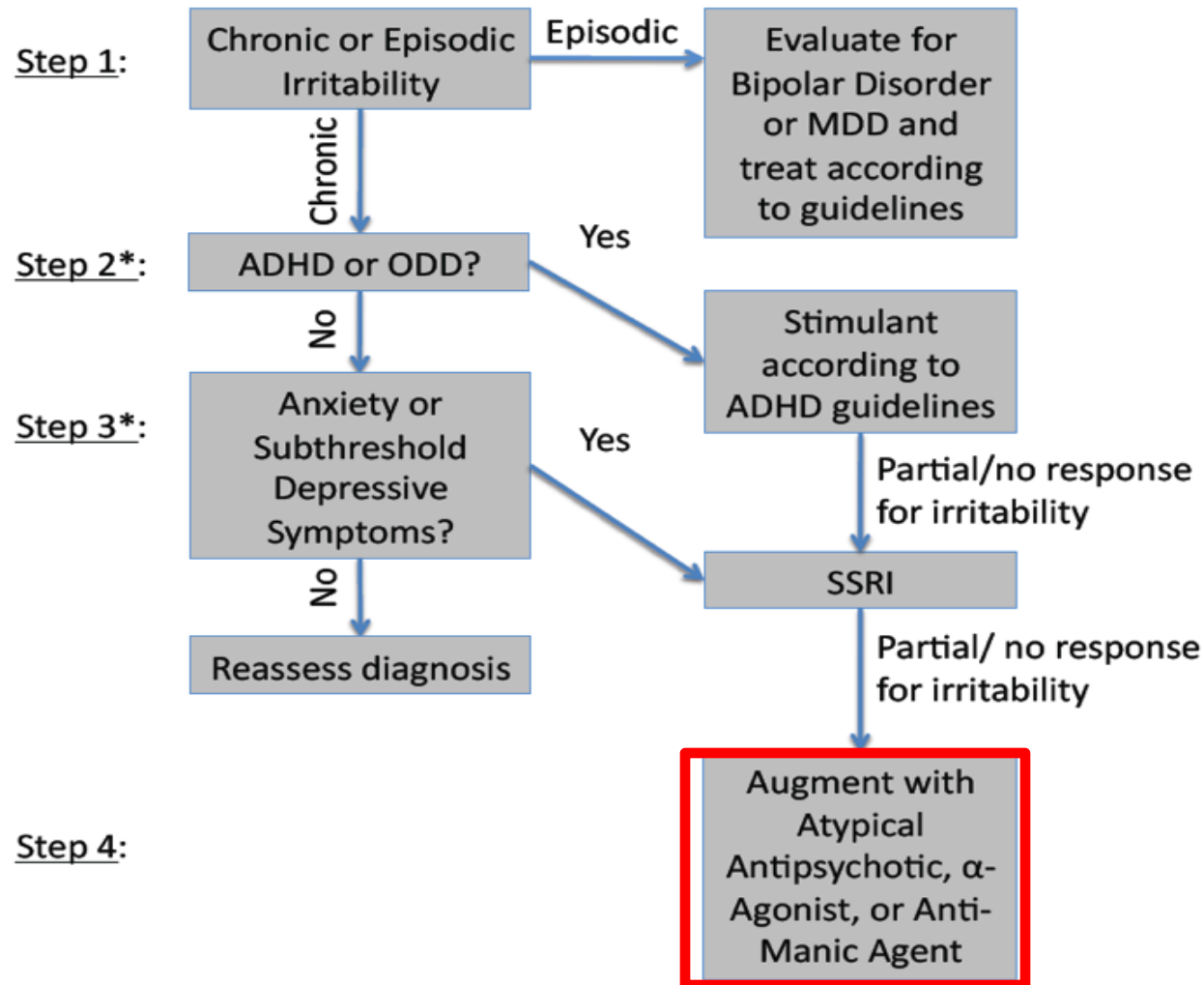
VS.

- **Manic switching:** “he has never been this way before”
 - Onset of new mood symptoms and behavior, vegetative signs
- **Management:**
 - Activation: lower dose, increase more slowly, different SSRI
 - Mood stabilizer, atypical antipsychotic

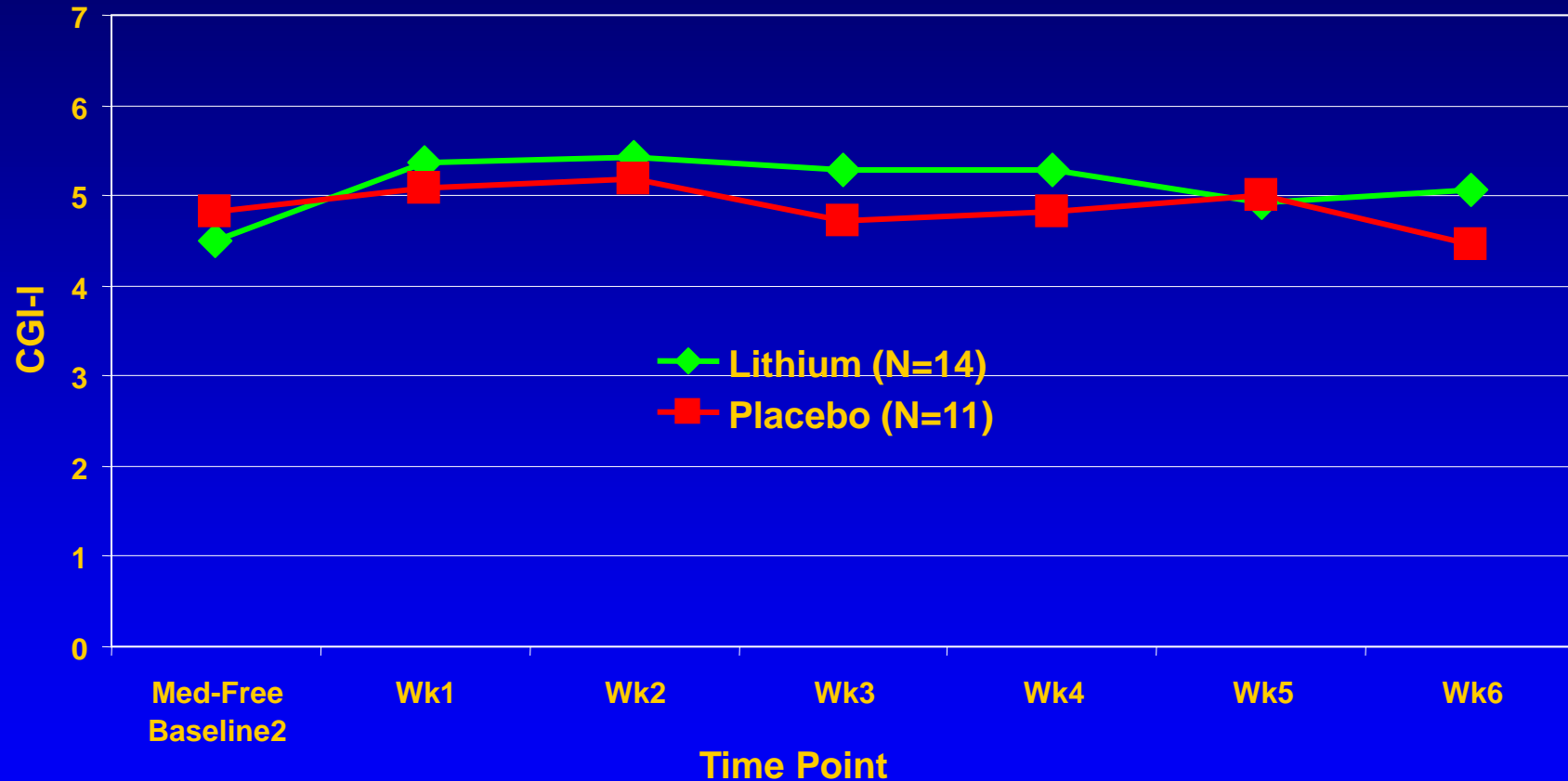
Rationale for stimulant + SSRI trial in SMD

- **High rate of anxiety disorders and ADHD in SMD**
- **As youth with SMD mature, increased risk for anxiety and MDD**
- **Evidence for efficacy of stimulants for both ADHD sx's and aggressive sx's**
- **More benign side-effect profile than antipsychotic medication**

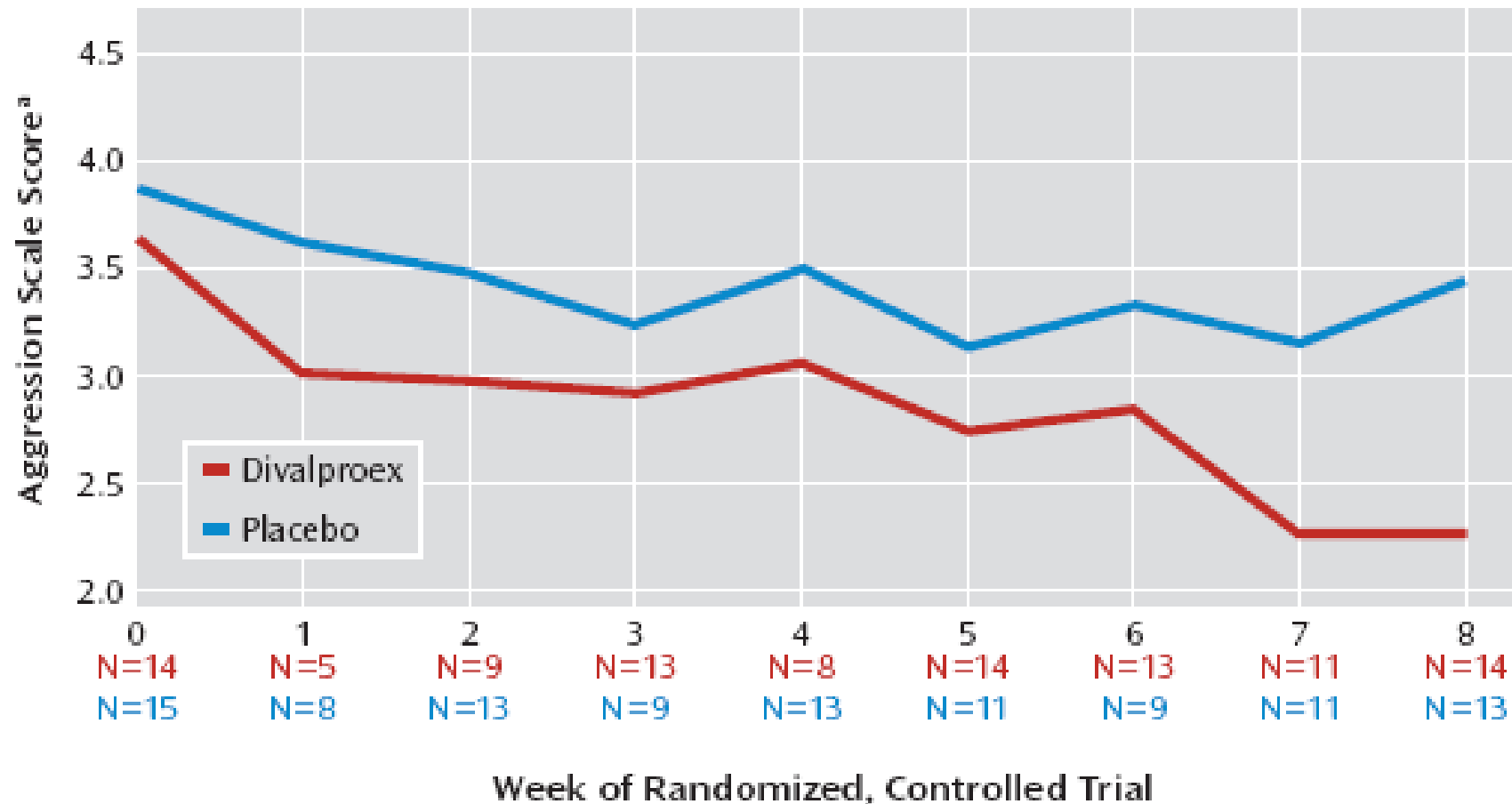
Irritability Treatment Algorithm



SMD Lithium RCT: CGI-I



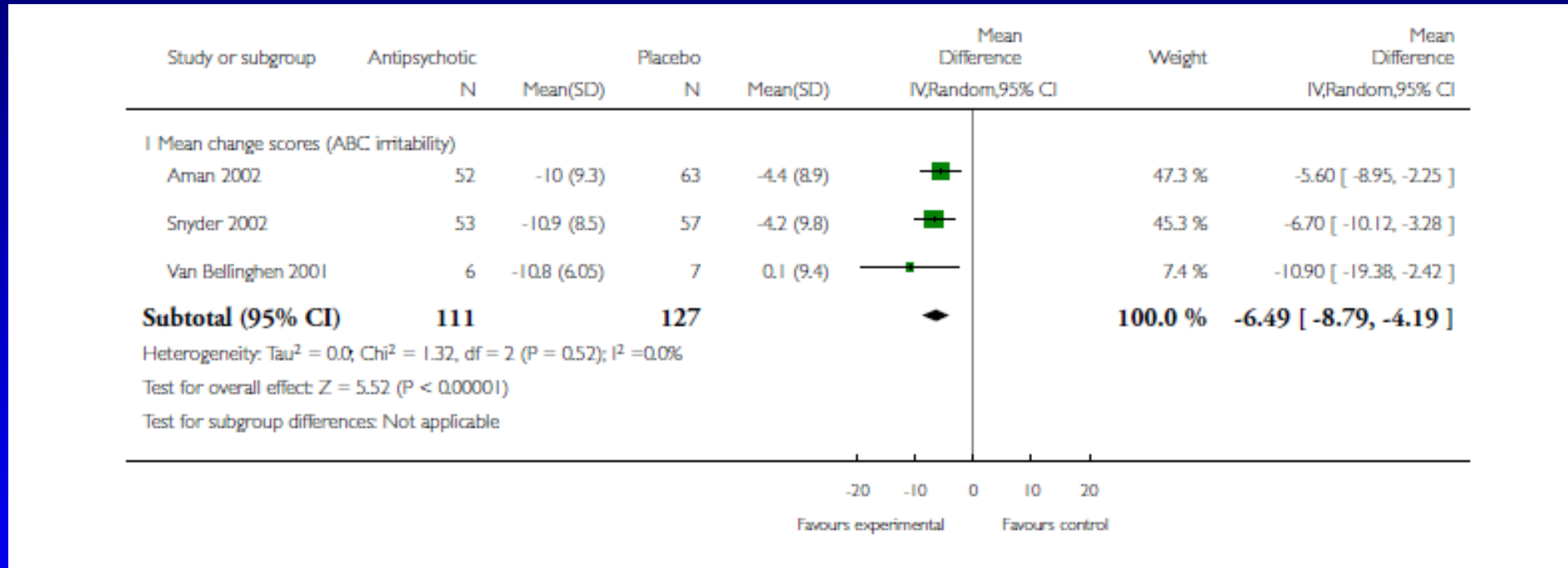
Stimulant plus divalproex vs. placebo in ADHD + aggression



All received concurrent behaviorally oriented psychosocial Rx
Mean age = 8.4 ± 2.0 years

Blader et al, 2009

Cochrane Report: Atypical antipsychotics for disruptive behavior disorders in youth

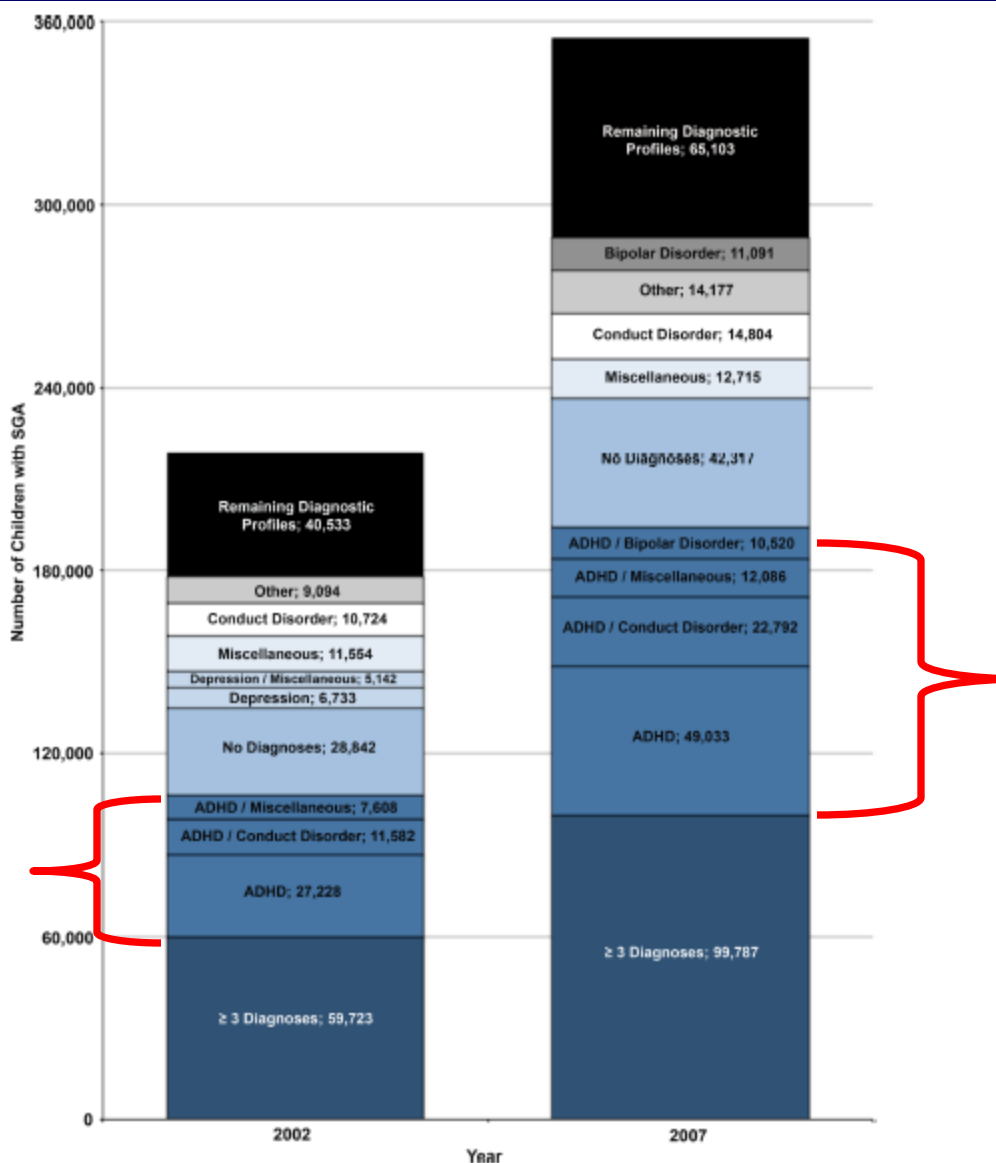


3 studies of risperidone, N=111

Difference on ABC irritability subscale “may be clinically significant”

Loy et al, 2012

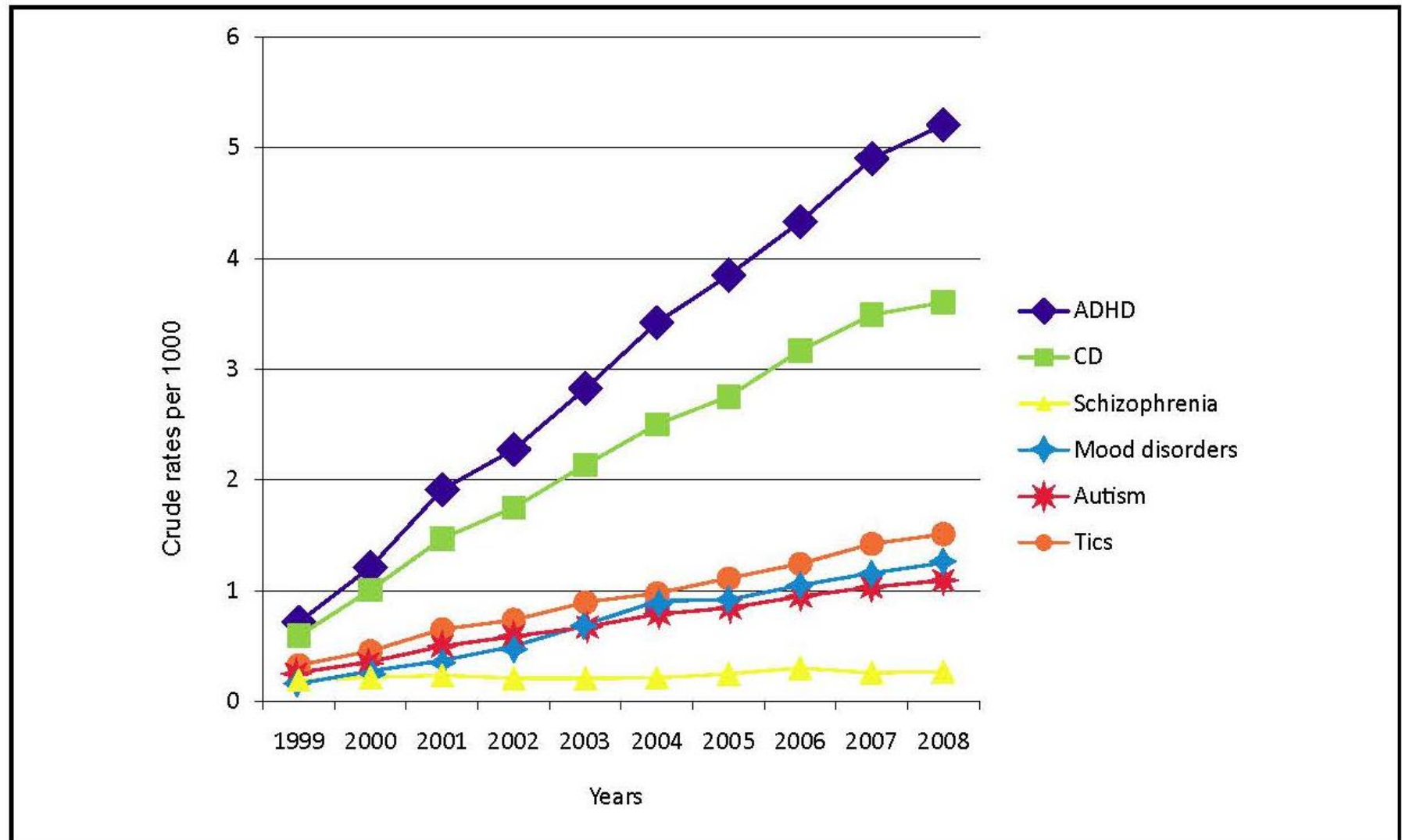
Diagnosis and SGA use in Medicaid-enrolled children 2002-2007



SGA use increased 62%, 2002-7
 In 2007,
 ADHD accounted for 50% of use
 1/7 had ADHD as only dx

Matone et al., 2012

Figure 4 Diagnoses linked to young antipsychotic users in the province of Manitoba



Summary

- **Severe non-episodic irritability (SMD) differs from BD in:**
 - longitudinal course: unipolar depression, anxiety (not bipolar disorder) in youth with chronic irritability
 - family history
- **Bipolar diagnosis should be reserved for youth with episodic symptoms.**
- **Treat the underlying illness (e.g., depression, anxiety, ADHD). Stimulants and SRI's not necessarily contraindicated.**