Treating Children with Anxiety and Bipolar Disorder

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NIMH
National Institute of Mental Health

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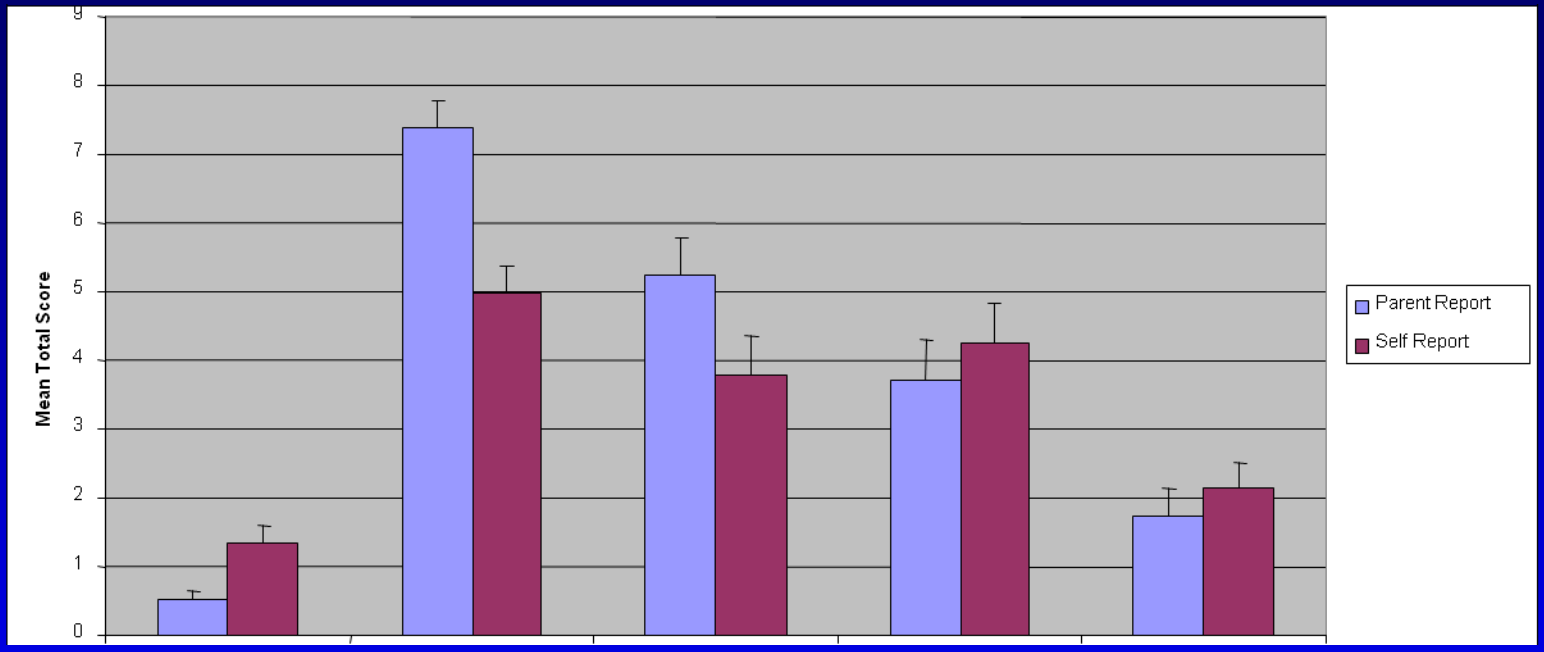
Talk Outline

- **Diagnosing bipolar disorder in children**
  - **In DSM, BD characterized by episodes**
  - **Is BD in children characterized by non-episodic, severe irritability?**
  - **No: research comparing youth with SMD vs. those with BD**
- **Anxiety in BD**
  - **Common comorbidity in adults and youth**
  - **Anxiety as a risk factor for BD**
- **Anxiety in SMD**
- **Treatment**

Irritability across diagnoses



Dx	Healthy	SMD	BD	Anxiety	At risk
N	77	67	35	39	35

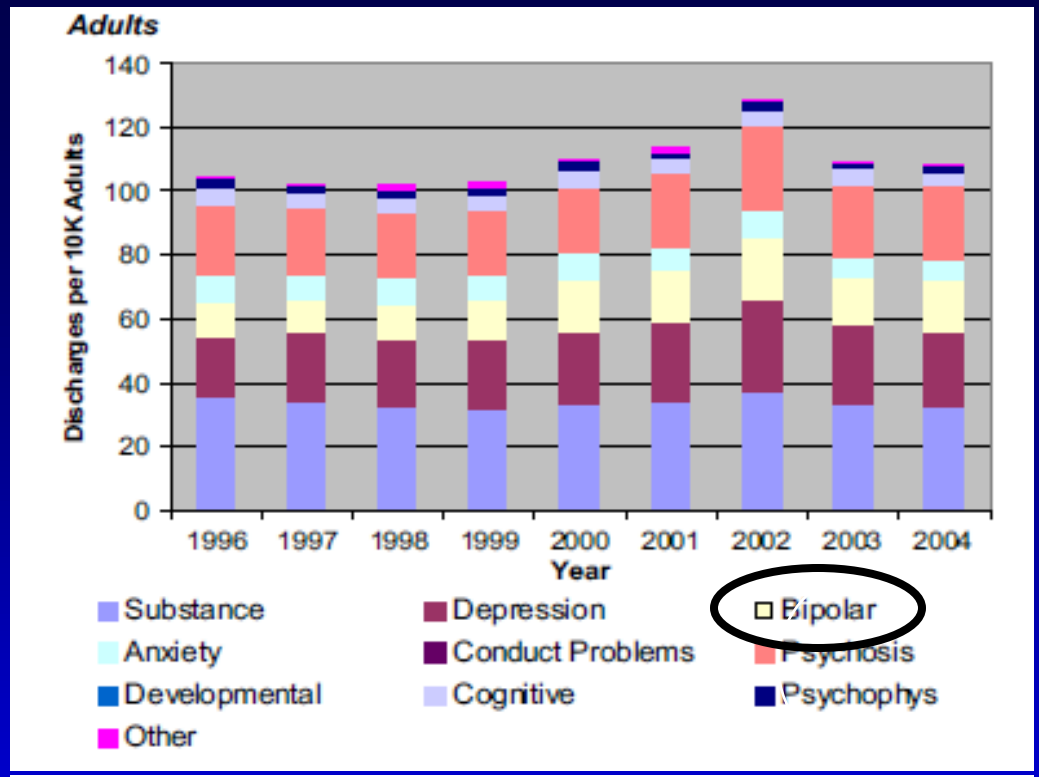
ANX>HV, At Risk; ANX=BD; ANX < SMD

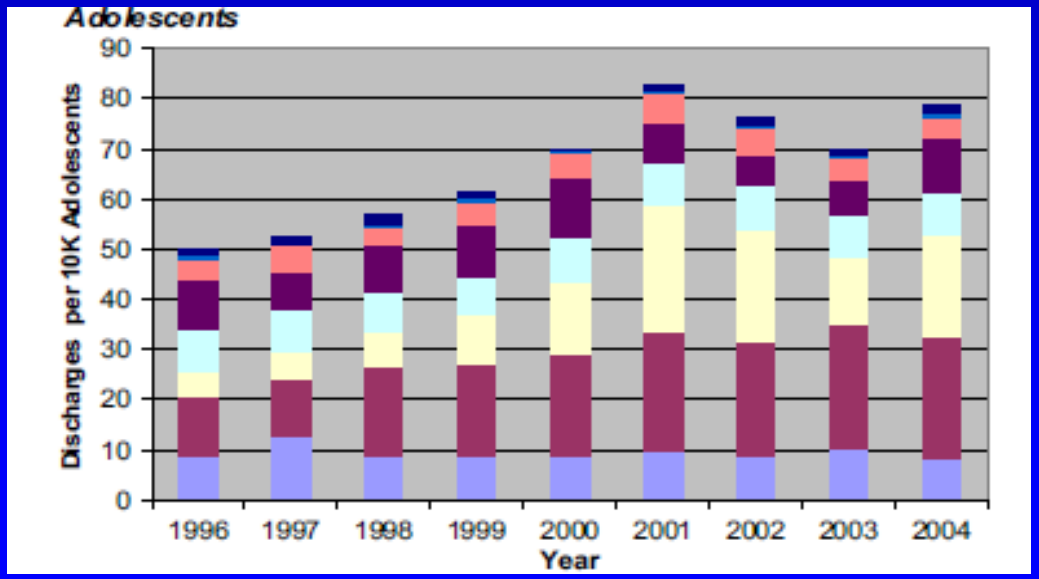
Stringaris et al, unpublished

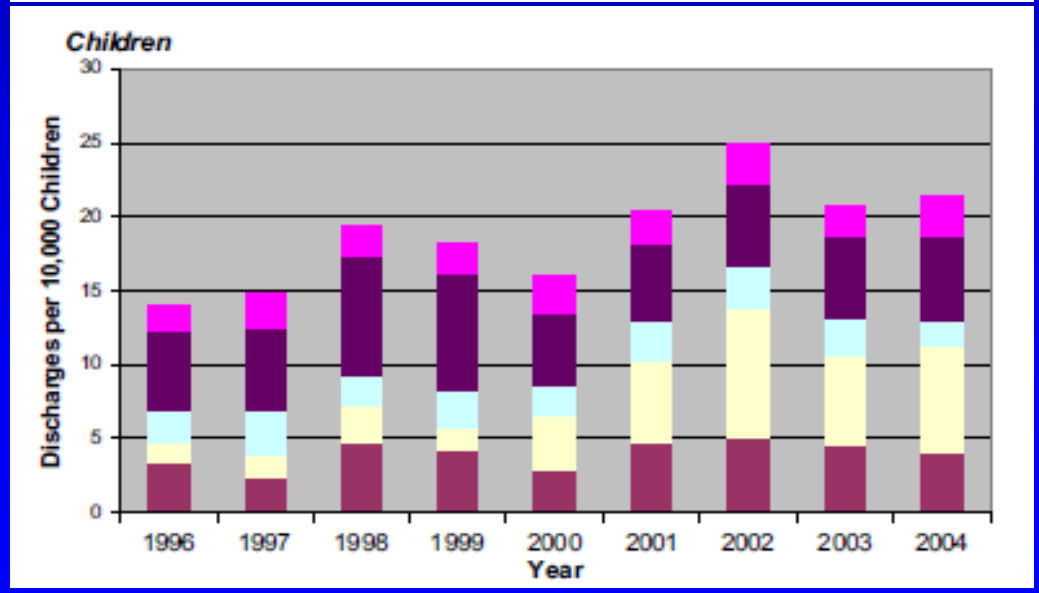
Diagnosing bipolar disorder in youth

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%)







Blader and Carlson, 2007

Diagnosing pediatric bipolar disorder: The controversy

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 ≥ 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 ≥ 1 week

B. Symptoms (3 of the following, or 4 if mood only irritable)
(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

All research groups "adhere to DSM-IV" BUT… the devil is in the details

"Developmental modifications" in diagnostic criteria for BD

Assumption: Youth with BD have cycles too rapid to be detected using adult techniques (Geller et al, 2004)

WASH-U: change definitions of episodes and cycles; cycles ≥ 4 hours

"B" criteria count even if they don't onset, or worsen, with mood change

Assumption: Instead of elation, youth with mania have very extreme irritability (Mick et al, 2005)

MGH: episode criterion waived if irritability is very severe

Research to address the controversy

- One can identify youth (including prepubertal youth) who meet classic criteria for bipolar disorder, as operationalized using DSM-IV

- 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 ≥ 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 = most severely impaired ADHD + ODD
  - Don't fit well in DSM-IV.
  - DSM-V TDD = SMD minus ADHD sx's

Interviewing tips

- Direct observation has the greatest weight
- Get lots of examples
- Interview parent and child separately and together
- Elevated mood, grandiosity are the trickiest
  - E.g. What is grandiosity in a 5, 10, 15, 25, 35 year old?
  - "The episode is your friend"….each children his/her own baseline.
- Ascertain episodes: worst mania, worst depression, euthymia
- ADHD etc. are diagnosed based on symptoms during euthymia.

Clinical characteristics	BD (N=118)	SMD (N= 134)
Age	12.9 ± 2.8	12.0 ± 2.0
Age of onset	9.8 ± 3.5	5.6 ± 2.2
Gender (% male)	52.0	69.7
% ADHD	57.0	85.3
% ODD	36.0	84.4
% Anxiety d/o	56.0	52.3
Number meds	2.4 ± 1.70	1.37 ± 1.45
% hospitalized	63.0	40.4
Children's Global Assessment Scale	51.1 ± 10.8	47.4 ± 9.0

Is SMD a developmental phenotype of BD?

- Longitudinal course (epidemiological studies)
- Family history
- Brain mechanisms of frustration, face emotion processing, other psychological mechanisms

What happens to children with SMD or severe irritability when they grow up?

Community-based studies:

- **Irritability in youth predicts anxiety, unipolar depression in adulthood**
  - **Duration of follow-up: 3 to 20 years**
- **Irritability in youth does not predict bipolar disorder in adulthood**

NIMH study:

- **Over two years, one SMD child out of 84 developed an episode**

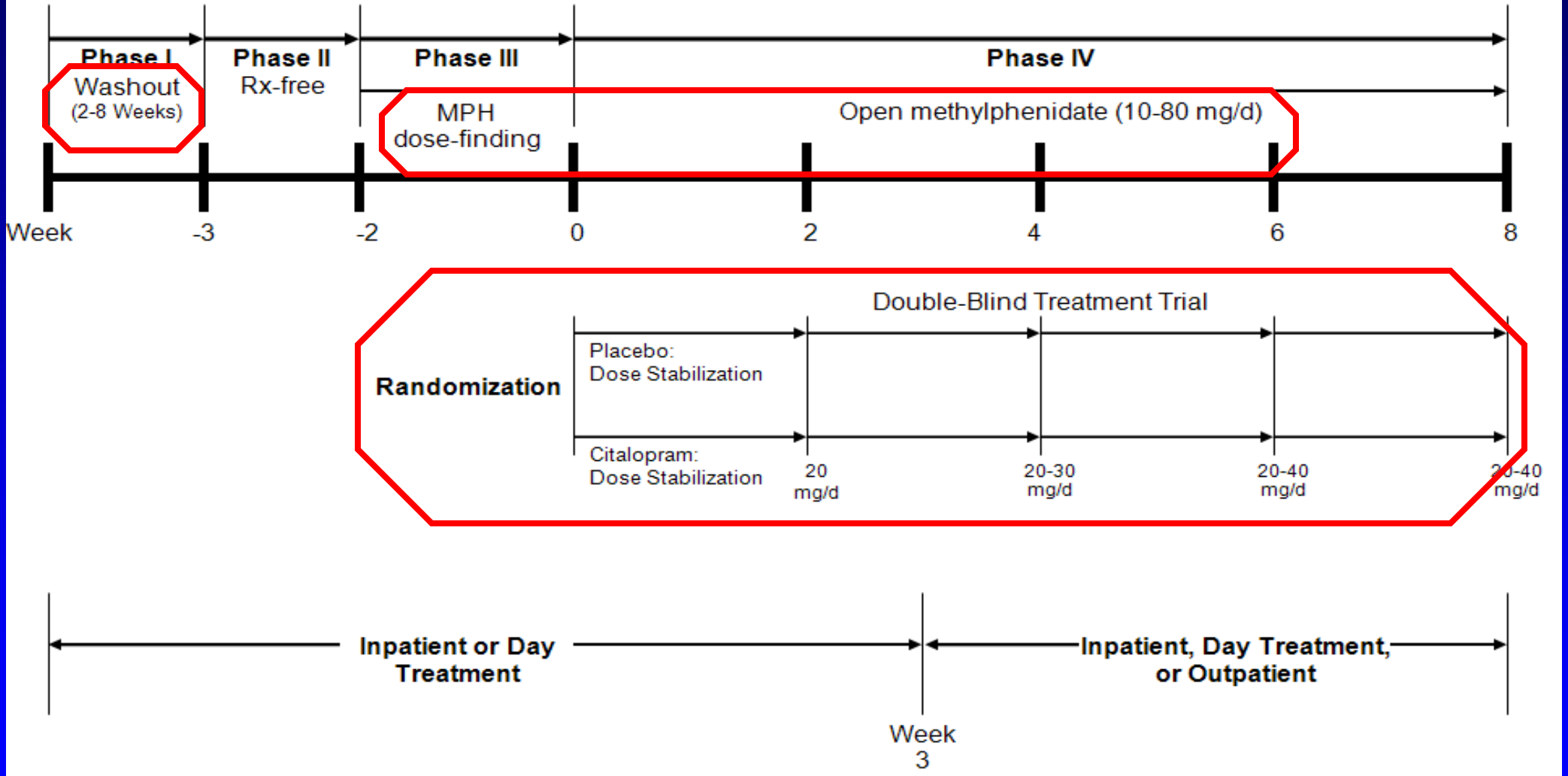
Family history

- Children with bipolar disorder tend to have a family history of bipolar disorder.
- Children with SMD are not particularly likely to have a family history of bipolar disorder.

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

- Treatment!!!
- If SMD = BD, then antipsychotic medication, anticonvulsants
- If SMD = ADHD + anxiety and/or depression, then stimulants and SRI's
  - Ongoing trial at NIMH

Citalopram + MPH vs. Placebo + MPH: Clinical Trial



Anxiety in BD and SMD

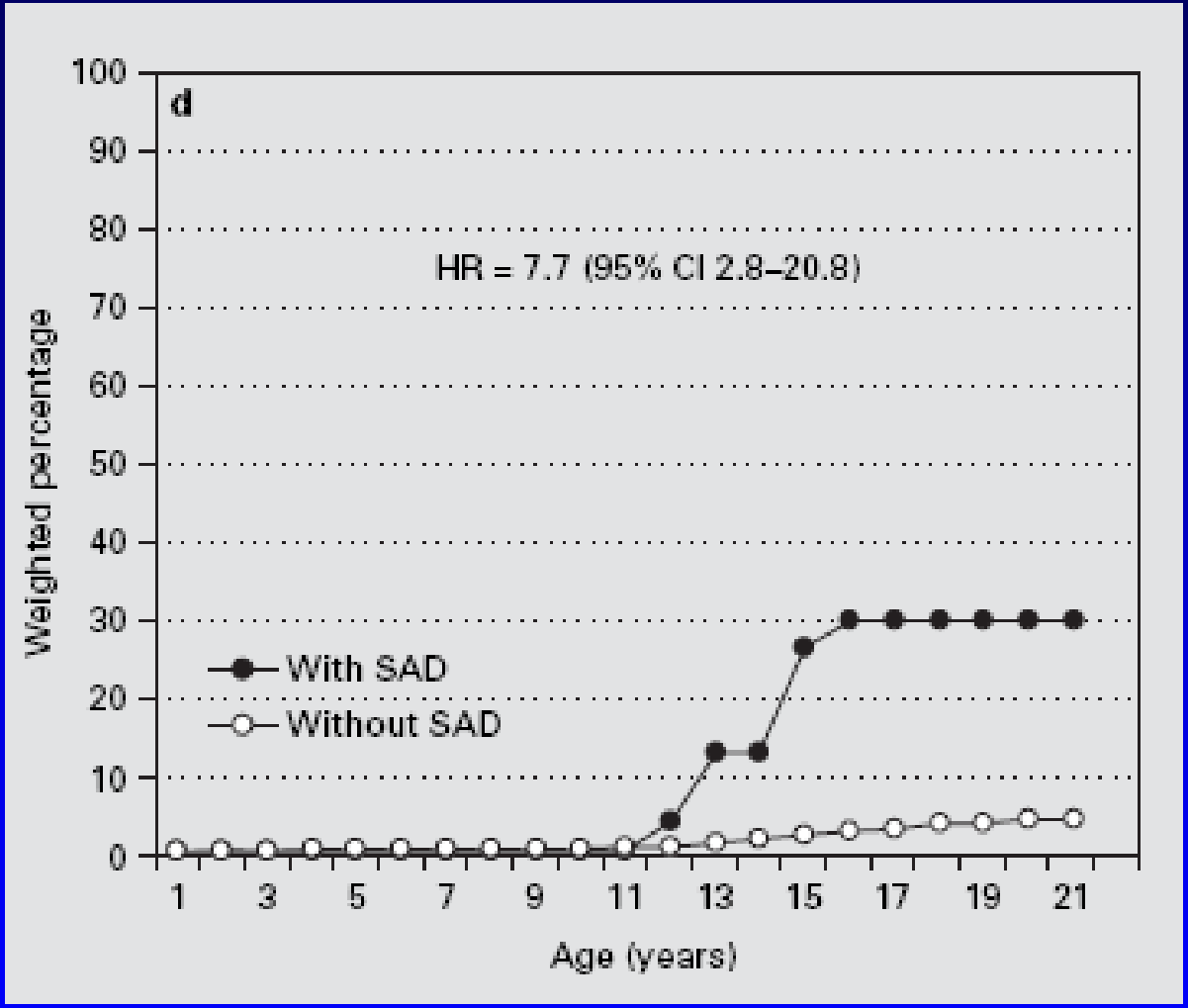
Comorbid anxiety disorders in youth with BD: Course of Bipolar Youth Study

Table 1. Total Sample and Comparison by Bipolar Subtype (BP-I, BP-II, and BP-NOS)*

Variable	All Subjects (N = 438)†	Subjects With BP-I (n = 255)†	Subjects With BP-II (n = 30)†	Subjects With BP-NOS (n = 153)†	Statistic	Overall Test *P* Value	Pairwise Comparisons: Effect Size (*d*) of Difference (*P* Value)‡ BP-I vs BP-II§	BP-I vs BP-NOS‖	BP-II vs BP-NOS¶
Lifetime history of comorbid disorders									
Any anxiety disorder	39.0	37.3	60.0	37.9	Wald $\chi^2 = 6.3$	.04	0.49 (.01)	0.03 (.80)	0.46 (.02)
ADHD	59.8	60.4	43.3	62.1	Wald $\chi^2 = 0.9$	.72	0.14	0.05	0.08
Conduct disorder	12.8	13.3	13.3	11.8	Wald $\chi^2 = 0.2$	.96	0.04	0.02	0.06
ODD	39.5	40.8	23.3	40.5	Wald $\chi^2 = 1.1$	.39	0.26	0.05	0.22
Substance use disorder	9.1	9.8	6.7	8.5	Wald $\chi^2 = 2.0$	.38	0.25	0.03	0.28
PDD	2.1	2.0	3.3	2.0	Wald $\chi^2 = 0.3$	.85	0.10	0.01	0.11

Axelson et al, 2006

Separation anxiety in youth as a risk factor for BD



N=1,910

Bruckl, 2007

Anxiety in youth as a risk factor for BD

TABLE 1. Prevalence of Full or Subthreshold Bipolar Disorder in a Random Community Sample of 717 Young Adults With and Without A History of Adolescent Psychiatric Disorder[a]

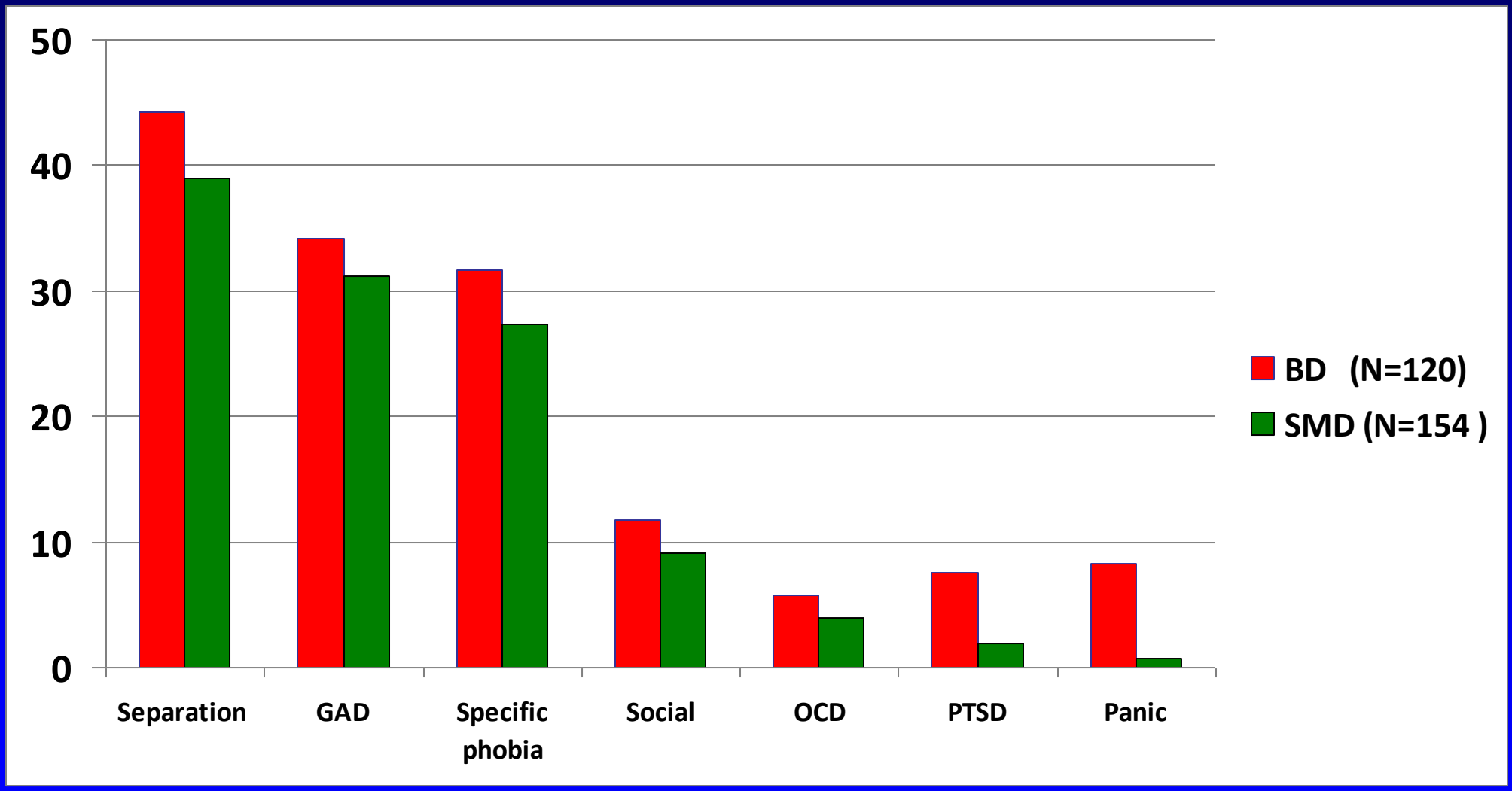
	Subjects With Adolescent Disorder			Subjects Without Adolescent Disorder			Analysis		
		Subjects With Full or Subthreshold Bipolar Disorder in Early Adulthood			Subjects With Full or Subthreshold Bipolar Disorder in Early Adulthood				
Adolescent Psychiatric Disorder	N	N	%	N	N	%	Odds Ratio	95% CI	p[b]
Anxiety disorder	52	6	11.5	665	18	2.7	4.69	1.78–12.38	<0.01[c]
Depressive disorder	53	5	9.4	664	19	2.9	3.54	1.27–9.88	<0.05
Disruptive disorder	81	6	7.4	636	18	2.8	2.75	1.06–7.13	<0.05
Personality disorder	156	9	5.8	561	15	2.7	2.23	0.96–5.19	n.s.
Substance use disorder	43	3	7.0	674	21	3.1	2.33	0.67–8.15	n.s.

[a] Mean age of young adult subjects=22 years (SD=3).
[b] Fisher's exact test.
[c] Association with full or subthreshold bipolar disorder in young adulthood remained significant after control for manic symptoms during adolescence.

N=665

Johnson et al, 2000

Anxiety diagnoses (%) in BD and SMD



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 ≥ 13*

***Labeling: consider other medications first**

Comparing mood stabilizers and 2nd generation antipsychotics: Efficacy

Outcome	Children and adolescents: SGA trials (n = 1,118)		MS trials (n = 494)		SGA versus MS in youth
Continuous outcome	**ES[e]**	**95% CI[e]**	**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[e]**	**95% CI[e]**	**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

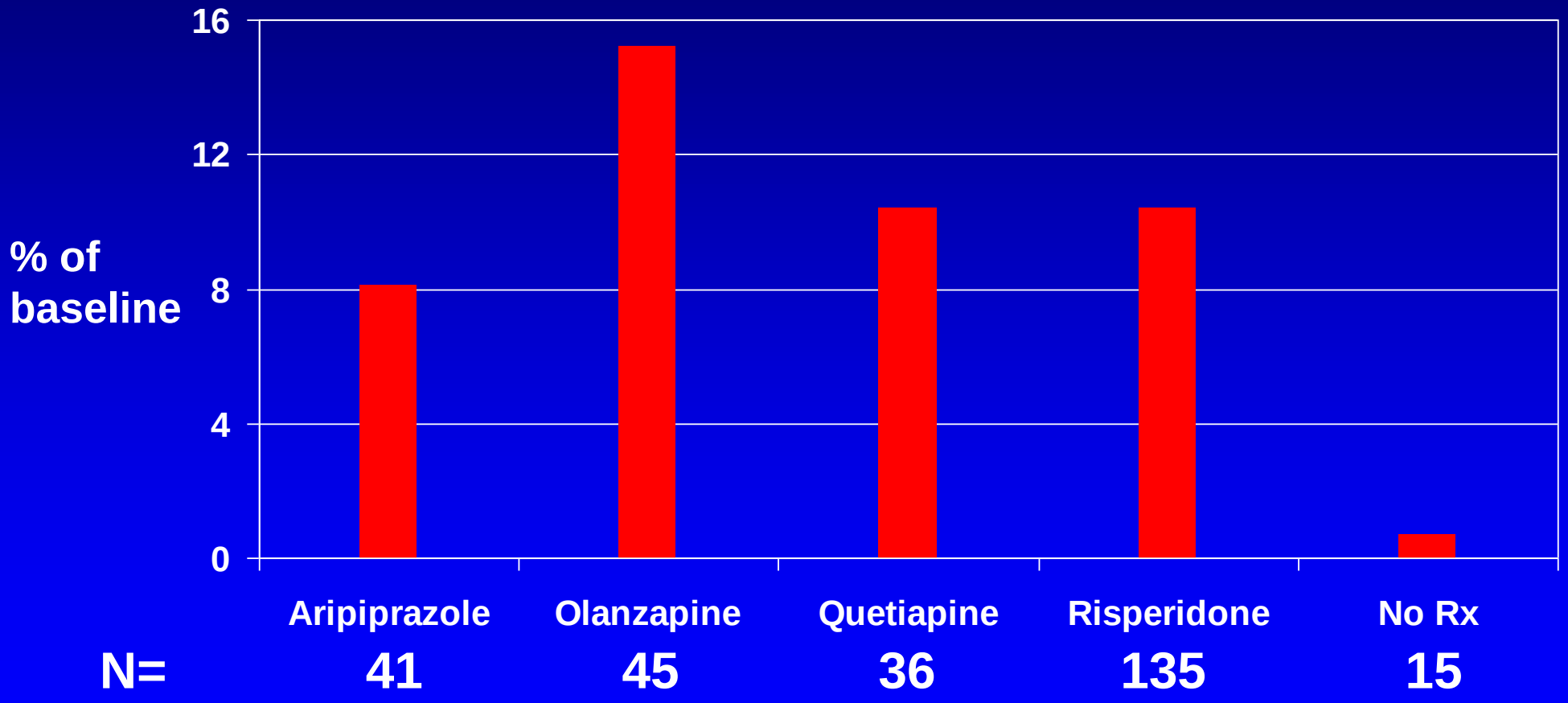
Correll et al, 2010

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

	Children and adolescents				
Outcome	SGA trials (n = 1,118)		MS trials (n^a = 494; n^b = 438)		SGA versus MS in youth
Continuous outcome	**ES**	**95% CI**	**ES**	**95% CI**	
Weight change	**0.53**	0.41–0.66	0.10[a,a]	–0.12–0.33	**SGA > MS**
			0.46[b]	0.24–0.72	NS
Categorical outcome	**NNH**	**95% CI**	**NNH**	**95% CI**	
>7% weight gain	**10.0**	7.5–14.9			
Somnolence	**4.7**	3.9–6.0	**9.5**	6.3–23.5	**SGA > MS**
Insomnia	100.0[a]	–47.1–24.0	15.1[a]	–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

Correll et al, 2010

Weight gain during first 11 weeks of Rx



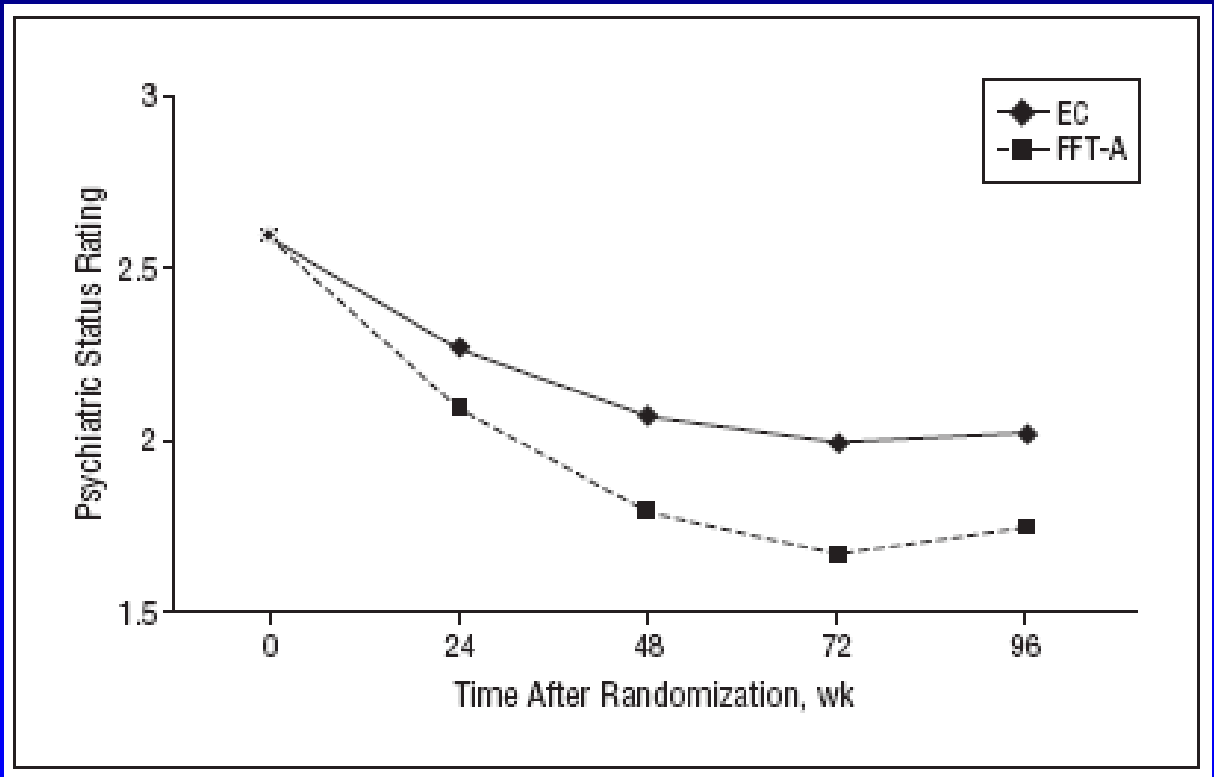
Mean age: 13.9 ± 3.6

Correll et al, 2009

Adjunctive family-focused treatment for adolescents with bipolar disorder

21 sessions in 9 months

psychoeducation, communication and problem solving skills training



N=58

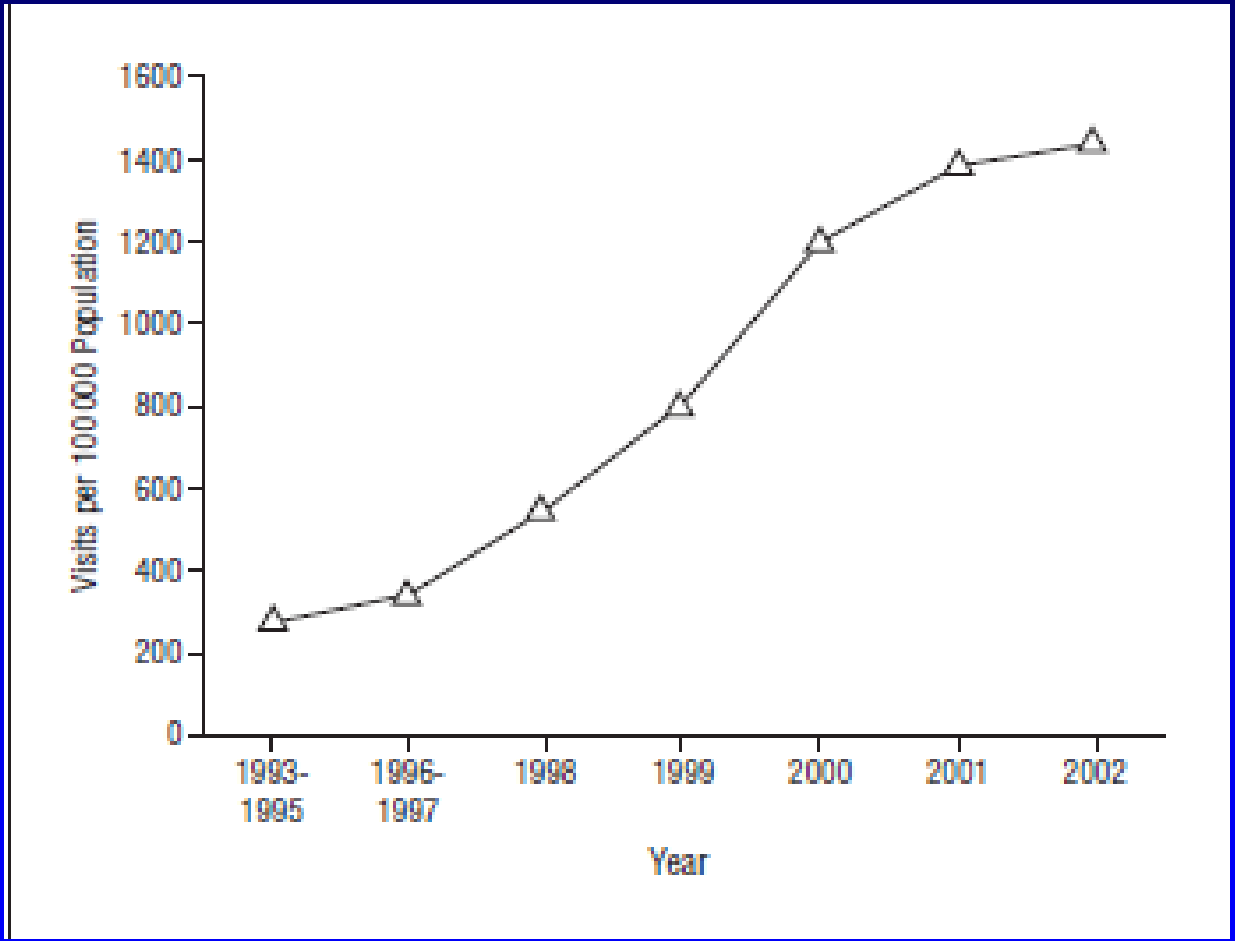
Miklowitz et al, 2008

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

Increase in antipsychotic drug prescriptions in children



Olfson et al, 2006

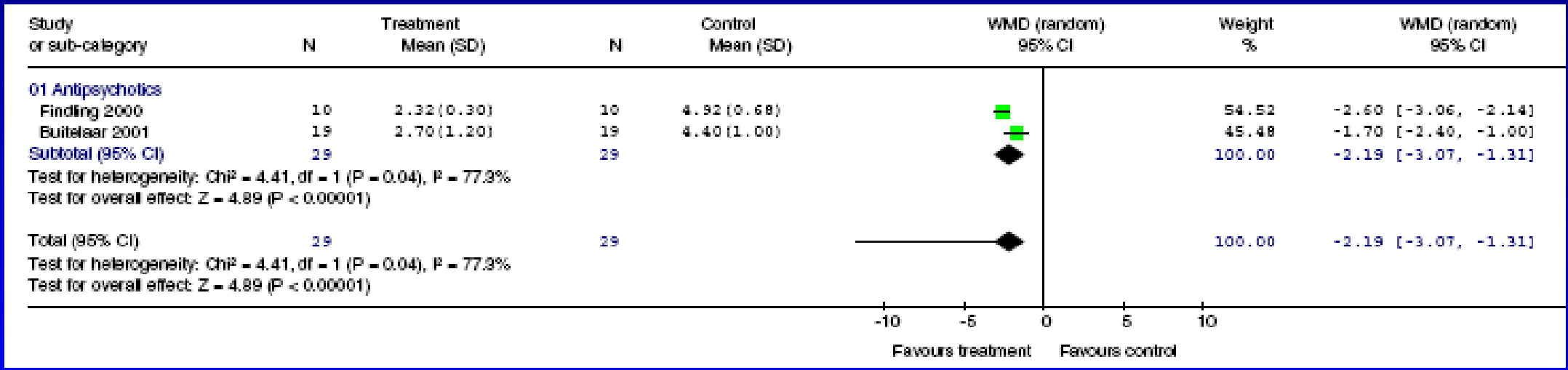
Diagnoses of children receiving antipsychotic medication

Table 2. Demographic and Clinical Characteristics of Office-Based Physician Visits by Children and Adolescents, 2000-2002*

Characteristic	Visits With Antipsychotic Treatment (n = 173)	Visits Without Antipsychotic Treatment (n = 1251)	χ^2 Statistic	*P* Value
Mental disorder diagnosis				
Psychotic disorder	27 (14.2)‖	27 (1.6)‖	8.5	<.001
Disruptive behavior disorder	70 (37.8)	647 (52.1)	3.0	.08
Mood disorder	48 (31.8)	255 (20.7)	3.4	.07
Tic disorder	9 (3.3)‖	23 (0.9)‖	2.1	.15
Pervasive developmental disorder or mental retardation	28 (17.3)‖	53 (3.7)	3.2	.08
Other mental disorder	68 (32.1)	387 (28.3)	0.8	.38

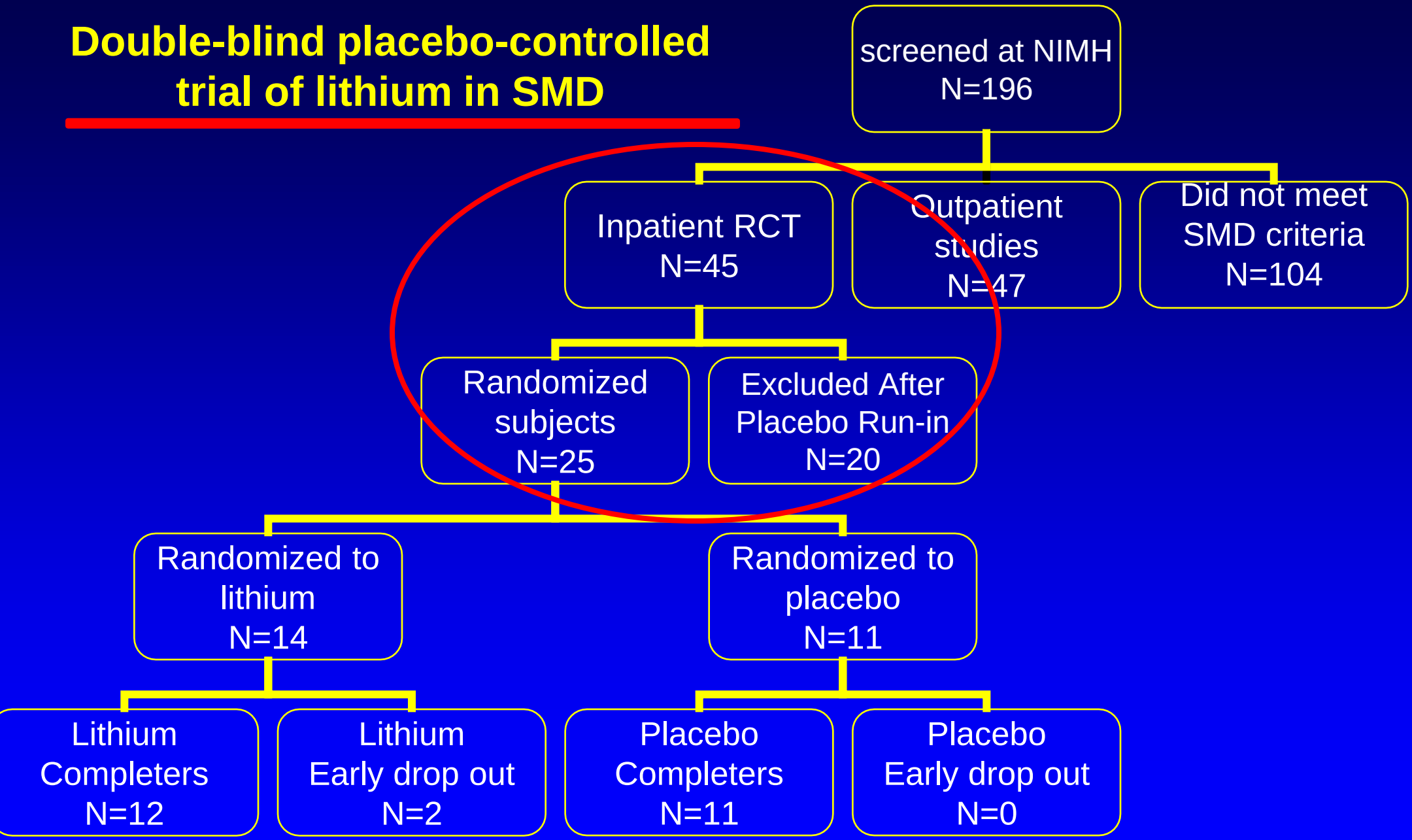
Olfson et al, 2006

Meta-analysis: Antipsychotic treatment in disruptive behavior disorders

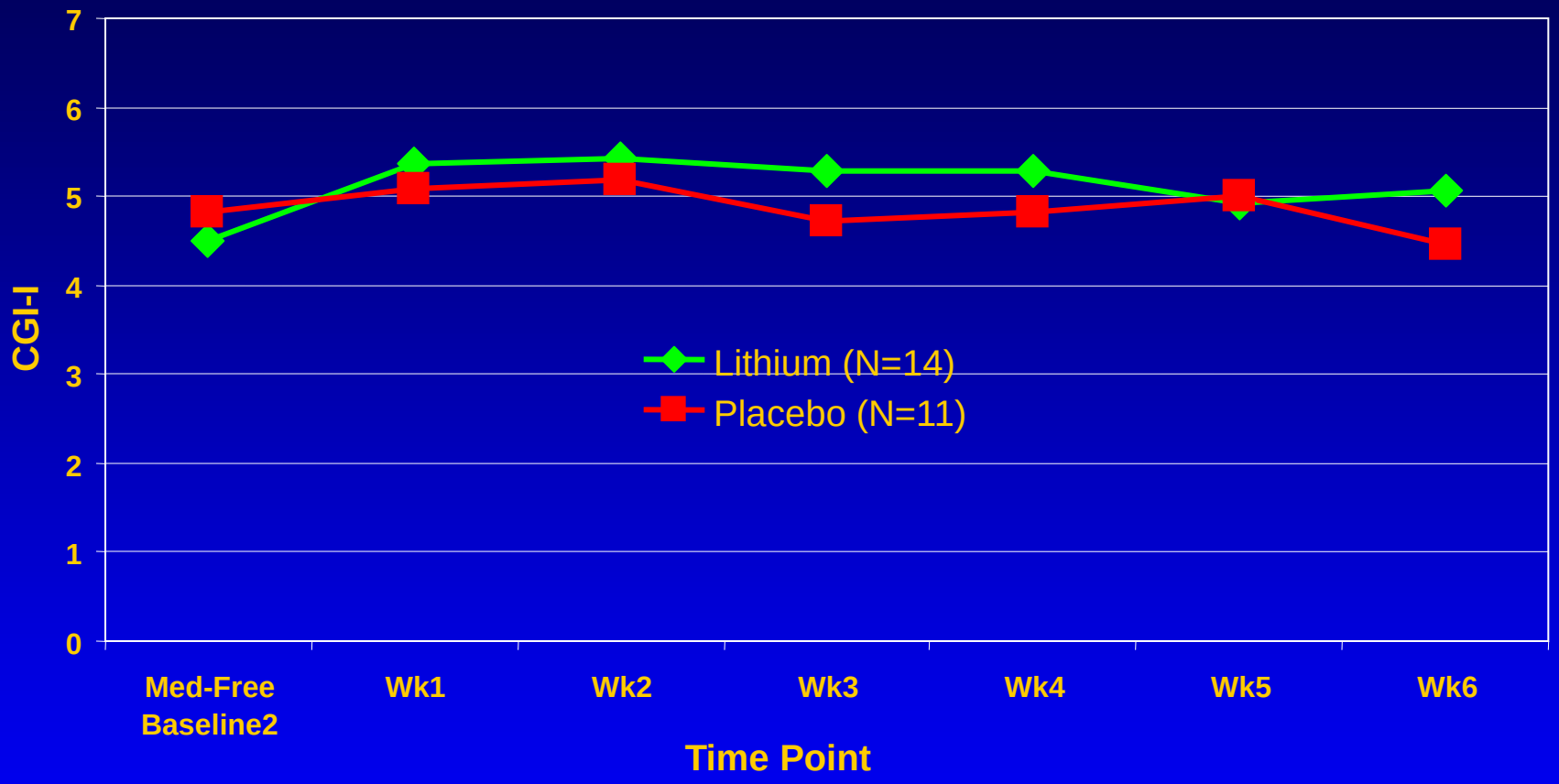


Ipser and Stein, 2007

Double-blind placebo-controlled trial of lithium in SMD

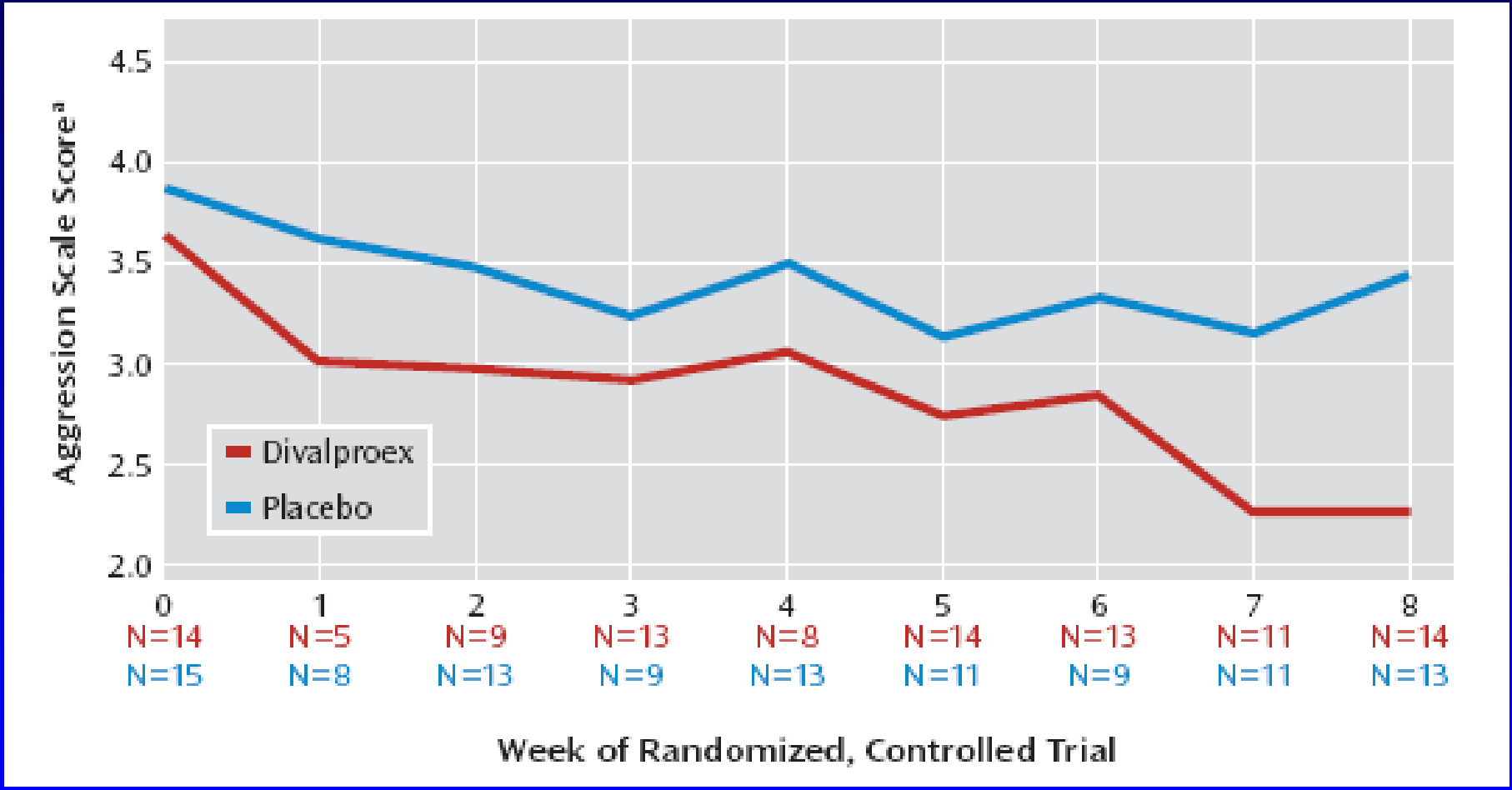


SMD Lithium RCT: CGI-I



- CGII<4 by trial's end Lithium (N=14) vs. Placebo (N=11) LogOR=1.00, Std Error=1.23, $\chi 2$=0.66, p=0.41.
  - 3/14 Lithium and 1/11 Placebo SMD

Stimulant plus divalproex vs. placebo in ADHD + aggression

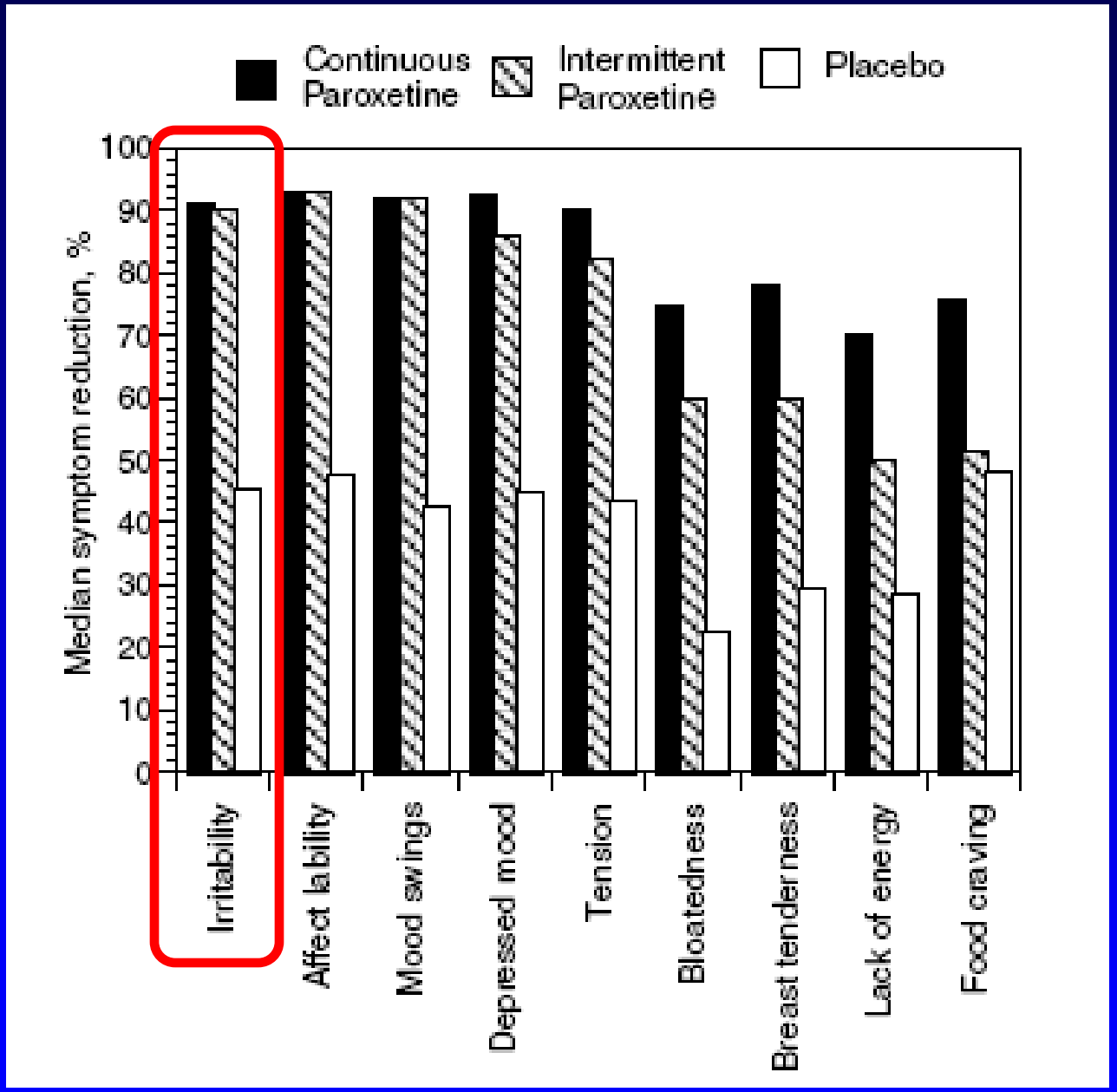


All received concurrent behaviorally oriented psychosocial Rx

Mean age = 8.4 ± 2.0 years

Blader et al, 2009

Irritability in PMDD responds to paroxetine



N=55/group
Landen et al, 2007

Fluvoxamine-induced activation

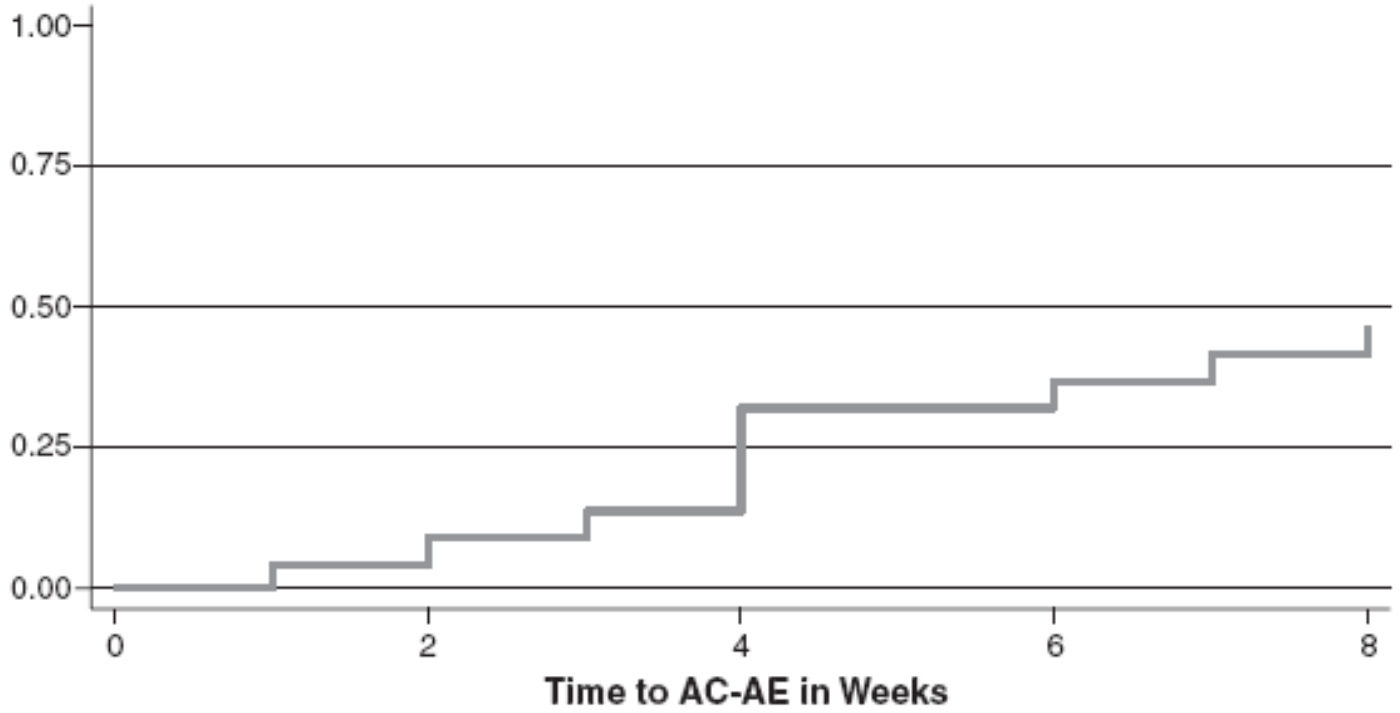


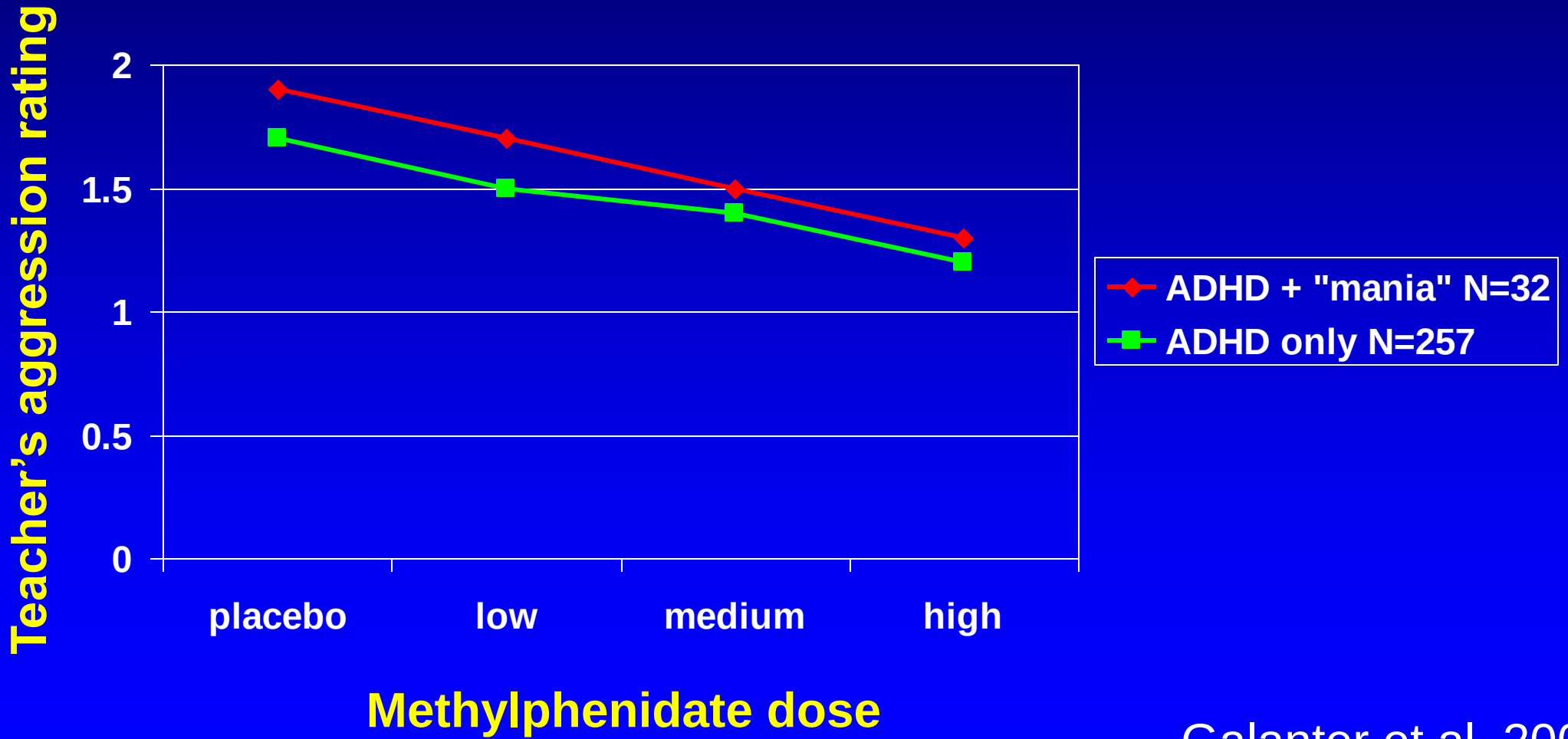
FIG. 2. The Kaplan–Meier estimate of the incidence of AC-AEs by week of fluvoxamine treatment. AC-AEs = Activation cluster–adverse events.

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

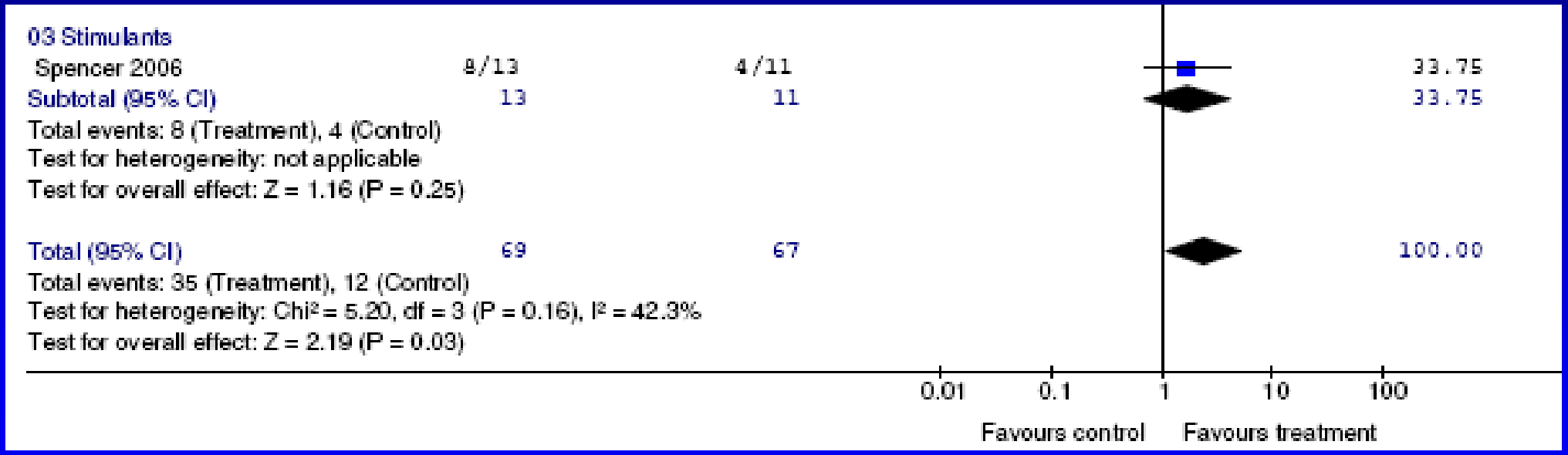
Reinblatt et al, 2009

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



Galanter et al, 2003

Stimulant treatment for disruptive behavior disorders in youth

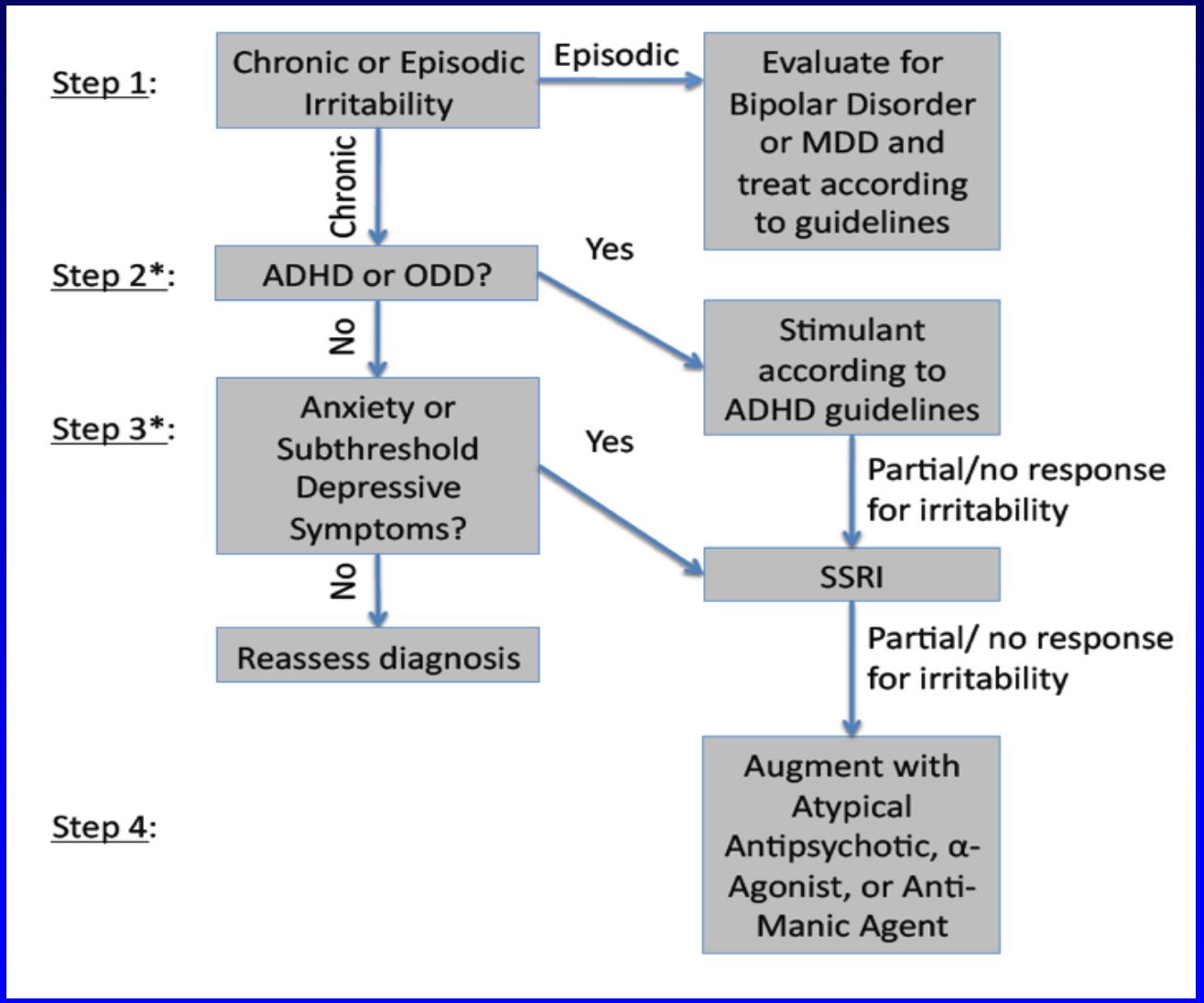


Ipser and Stein, 2007

Psychotherapeutic treatments of oppositionality or aggression

- Parent-child interaction therapy for oppositional children
- The Incredible Years Parents, Teachers and Child Training Series for conduct problems
- Group anger control training for aggression
- Multisystemic therapy for willful misconduct

Irritability Treatment Algorithm



Hulvershorn and Dickstein, 2011

Anxiety in BD or SMD: Implications for treatment

- **Anxiety in BD**
  - **Concerns re: use of SSRI unless "covered" by mood stabilizer or SGA**
- **Anxiety in SMD**
  - **Treat anxious youth with irritability as you would anxious youth without irritability**
  - **Difference in response?**

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

- Treatment!!!
- If SMD = BD, then antipsychotic medication, anticonvulsants
- If SMD = ADHD + anxiety and/or depression, then stimulants and SRI's
  - Ongoing trial at NIMH

Conclusions

- Severe, non-episodic irritability (SMD) differs from episodic BD in longitudinal course, outcome, family history, and pathophysiology.
- Severe irritability in youth predicts unipolar depression and anxiety disorder in adulthood.
- Anxiety disorders are common in both SMD and BD.
- More research is needed on both pharmacologic and psychotherapeutic approaches to both SMD and BD.

DO YOU HAVE A CHILD WITH Bipolar Disorder or *Severe Irritability?*

At the NIH Clinical Center in Bethesda, Maryland, several research studies are being conducted into the **causes of bipolar disorder or severe irritability.**

These studies seek children and adolescent participants ages 6-17 who have bipolar disorder or severe irritability.

All evaluations, research procedures, and inpatient/day hospital care are free of cost. Children and parents are compensated for participation.

Travel expenses are paid, and both parent and child must agree to the child's participation.

CAUSES OF BIPOLAR DISORDER

Participant Criteria:

- Ages 6-17 with bipolar disorder
- Able to perform research tasks that include: neuroimaging, computer tasks, and neuropsychological testing

A) Non-Treatment Study:

If stable on current medications:

- Receive annual outpatient visits

B) Two Different Treatment Studies:

If unstable on current medications, day or full hospitalization to discontinue medication

- Parent and clinician together choose either:

1) Perform research tasks while medication-free for 2 weeks, followed by standard medications.

2) Clinical trial of riluzole vs. placebo

- Ages 9-17 with bipolar disorder
- Have not done well on mood stabilizer and/or atypical antipsychotic drugs alone or in combination

Protocol #: 00-M-0198 & 09-M-0042

CAUSES OF SEVERE IRRITABILITY

Participant Criteria:

- Ages 7-17
- Have irritability symptoms that include: difficulty handling frustration (severe temper tantrums and rages) and "hyper" behavior (distractible, hyperactive, trouble sleeping)
- Able to perform research tasks that include neuroimaging, computer tasks and neuropsychological testing

A) Non-Treatment Study:

If stable on current medications:

- Receive annual outpatient visits

B) Treatment Studies:

If unstable on current medications:

- Receive day or full hospitalization to discontinue medication
- Parent and clinician together choose either:

1) Perform research tasks while medication-free for 2-weeks, followed by standard medications

2) Study the efficacy of methylphenidate plus citalopram, vs methylphenidate plus placebo, for decreasing irritability in children with severe mood and behavioral problems

- This study lasts 12 to 15 weeks
- If clinically appropriate, participants who received methylphenidate plus placebo will be offered the opportunity to receive methylphenidate plus citalopram at the end of the study

Protocol #: 02-M-0021 & 09-M-0034

BiPOLARKids
RESEARCH STUDIES at NIMH

CALL TO PARTICPATE **301-496-8381**
TTY: 1-866-411-1010

Ellen Leibenluft, M.D. or Kenneth Towbin, M.D. Email: bipolarkids@mail.nih.gov

NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH & HUMAN SERVICES

NIMH National Institute of Mental Health

BD,
SMD,
at risk for BD

Case #1

"Tim," a bright 11-year-old boy, was first seen by a psychiatrist at age 5 for distractibility, intrusiveness, peer difficulties, and excessive worry about harm coming to his parents. He was diagnosed as having attention deficit hyperactivity disorder and separation anxiety disorder. Treatment with stimulants alleviated his attentional symptoms for a time. At age 7,after his family moved, Tim exhibited sadness, social withdrawal, increased anxiety, and decreased appetite. These symptoms resolved spontaneously after approximately 2 months. At age 8, Tim was psychiatrically hospitalized for treatment after staying up nearly all night for a week. At that time, he was very excited because he believed he was a new Superhero called "Tigerman." He was convinced that he was growing whiskers and a tail and could outrun everyone. During this time, Tim ran around the house, growling, jumping on furniture, laughing and repeating the phrase "Tigger Timmy to the rescue!" At school, Tim was unable to sit and pay attention in class and was sent home early several times. His euphoria, grandiosity, and decreased need for sleep were uncharacteristic for him, and his distractibility, intrusiveness, and talkativeness were noticeably more marked than usual.

Case # 1 questions

1) Diagnosis?

2) How do you assess for the presence of comorbid anxiety?

3) What is first-line treatment? Second line?

4) How would the presence of comorbid anxiety impact on treatment?

Case #2

"Timothy," a bright 11-year-old boy, was first seen by a psychiatrist at age 5 for distractibility, intrusiveness, peer difficulties, and excessive worry about harm coming to his parents. He was noted to have an extremely "short fuse," and was unable to remain in several different preschools because of his disruptive behavior. He was diagnosed with ADHD, oppositional defiant disorder, and separation anxiety disorder. Treatment with stimulants alleviated his attentional symptoms for a time. At age 7, after his family moved, Tim exhibited sadness, social withdrawal, increased anxiety, and decreased appetite. These symptoms resolved after 2 months. However, his temper outbursts continued, so that his family felt as if they had to always "walk on eggshells" and other children didn't want to play with him. At school, Tim was unable to sit and pay attention in class. He would have verbal and, occasionally, aggressive outbursts when frustrated. He was often sent to the principal's office and sometimes sent home early. If disciplined, he would say that he was right, the teacher was wrong, and that he was smarter than she. At age 8, after his family moved again, his outbursts intensified and he was hospitalized psychiatrically.

Case # 2 questions

1) Diagnosis?

2) What is first-line treatment? Second line?

3) How would the presence of anxiety impact on treatment?