

ADULT ADHD

Approaches to Evaluation and Treatment

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DIAGNOSIS OF ADHD: TIMELINE

- 1968 Hyperkinetic Reaction of Childhood (DSM-II)
- 1980 DSM-III: Age of Onset Criteria set at age 7 (committee)
- 1987 DSM-III-R: Age of Onset Criteria remains at age 7 (small field trial)
- 1993 Kate Kelly and Peggy Ramundo publish “You Mean I’m Not Lazy, Stupid or Crazy? A Self Help Book for Adults with Attention Deficit Disorder,” and Thom Hartmann publishes “Attention Deficit Disorder: A Different Perception”
- 1994 DSM-IV: AOC remains at age 7, but must also produce impairment; additional field trials
- 1994 Edward Hallowell and John Ratey publish “Driven to Distraction: Recognizing and Coping with Attention Deficit Disorder from Childhood through Adulthood”
- 1995 Kevin Murphy and Suzanne LeVert publish “Out of the Fog: Treatment Options and Coping Strategies for Adult Attention Deficit Disorder,” Hallowell and Ratey publish “Answers to Distraction,” and Sari Solden publishes “Women with Attention Deficit Disorder: Embracing Disorganization at Home and in the Workplace”

A teenage patient recently told me his teacher makes fun of kids with ADD, saying all kids with ADD are lazy and use it as an excuse not to do their work. Such comments are inaccurate, and they are damaging.

Amen, 1995

“It’s not everybody who’s a goof-off and can’t keep a job. It’s not everybody who didn’t study for the test and has now declared that they’re learning-disabled and ADHD and need two hours longer to take their exam.

Pellock, 1995

ADHD: BOTH UNDER DIAGNOSED AND OVER DIAGNOSED

- Under Diagnosis:
 - Only 43% of cases treated (Anderson 1987)
 - Only 25-40% of cases diagnosed, 21-32% treated (Wolraich 1996)
- Over Diagnosis:
 - Only 72% of diagnosed cases met criteria

(Wolraich 1990)

ADHD

Diagnostic Criteria

- 6 of 9 symptoms (in either the Inattention or Hyperactivity-Impulsivity cluster)
- Some symptoms causing impairment before age 7
- Impairment in 2 or more settings
- Clear evidence of clinically significant impairment in social, academic, or occupational spheres
- Not due to another disorder

ADHD SYMPTOM CLUSTERS

Inattention

- Failure to attend to detail, careless mistakes
- Difficulty sustaining attention
- Doesn't listen
- Poor follow-through, failure to finish
- Difficulty organizing tasks and activities
- Avoidance of effort-demanding tasks
- Losing things
- Easily distracted
- Forgetful in daily activities

ADHD SYMPTOM CLUSTERS

Hyperactivity-Impulsivity

- Fidgets, squirms
- Unable to remain seated
- Runs or climbs excessively (restless in adults)
- Inability to play (relax) quietly
- “On the go,” “driven by a motor”
- Talks excessively
- Blurts out answers
- Can’t wait turn
- Interrupts, intrudes

ADHD: PREVALENCE

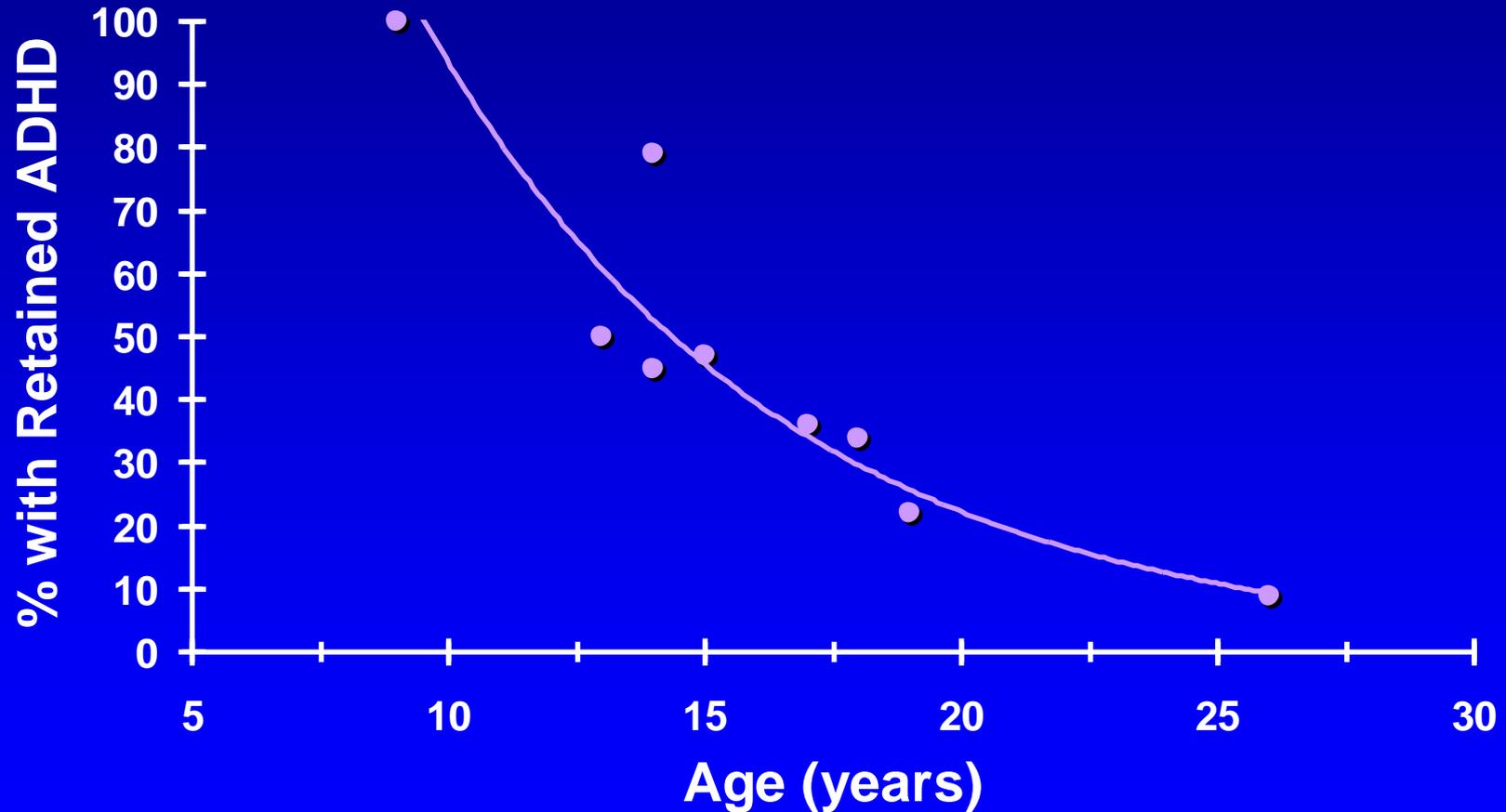
- Children (8 studies with $n > 500$)
 - 2.6-16% (Median 7%)
- Adults (8 follow-up studies of child cohorts)
 - 22-72% persistence (0.5-12% prevalence)
- Adults (3 survey studies)
 - 4-5% prevalence
- Because DSM-IV Criteria are “looser” and allow pure inattentive ADHD, figures could rise (and disproportionately so in adults)

ADULT ADHD

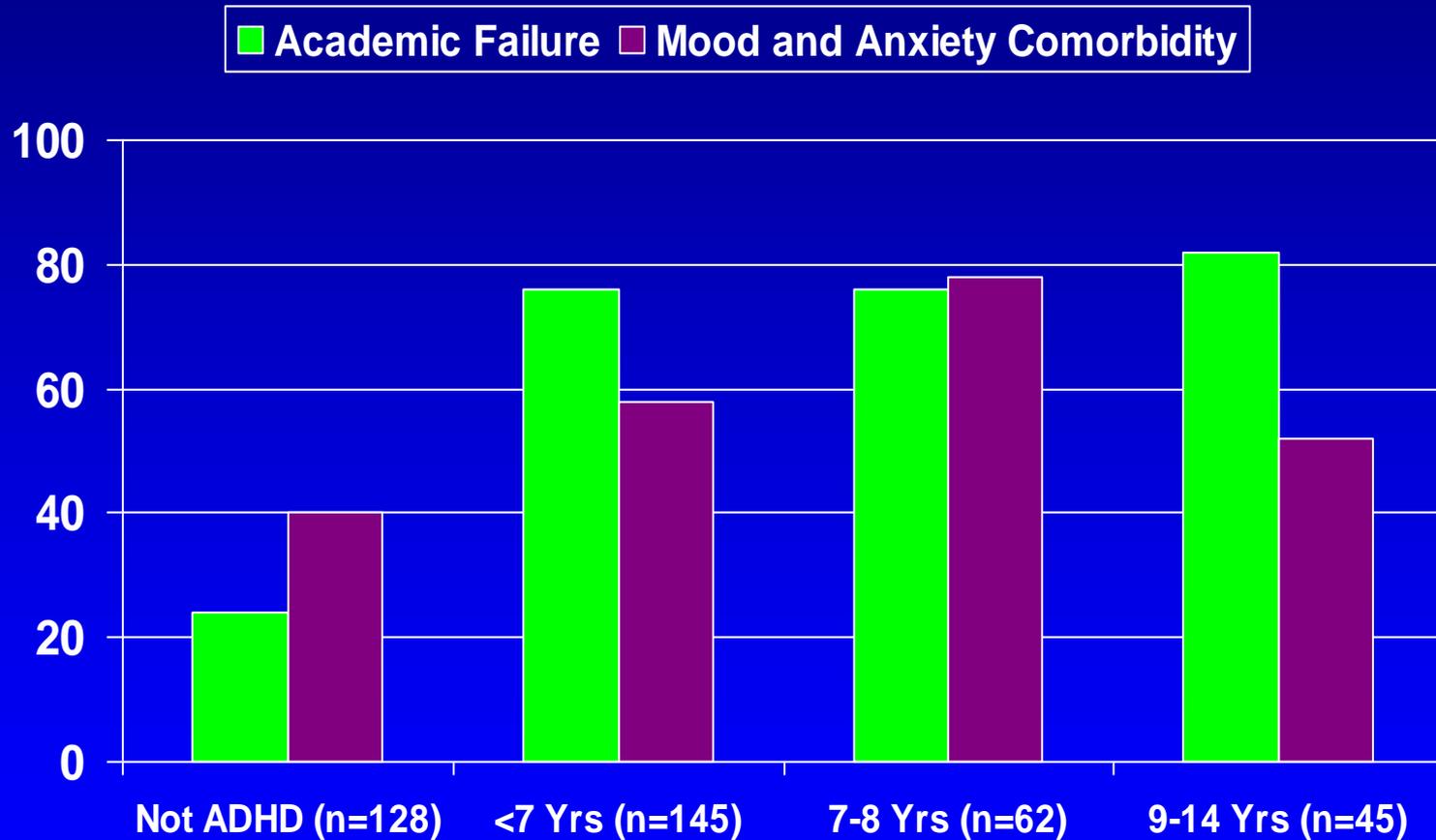
Prevalence Estimates Differ by Expert

- Shaffer 1994
0.25%
- Biederman 1993 2–5%

PERCENTAGE OF RETAINED ADHD DIAGNOSIS AS A FUNCTION OF AGE



ADHD: AGE OF ONSET CRITERIA ARE ARBITRARY



ADHD:

Subtypes Or Distinct Disorders?

- Inattentive
- Academic Problems
- “Internalizing” Disorders
- Increased LD (Self & Family)
- Input Problems
- Trails, Stroop, Letter Cancellation
- Posterior Hemisphere
- Lower Stimulant Response
- Lower Stimulant Doses
- Female
- Hyperactive/Impulsive
- Behavior Problems
- “Externalizing” Disorders
- Output Problems
- CPT, WCST
- Anterior Hemisphere
- Male

ADULT ADHD

Psychiatric Comorbidity

- Conduct disorder 30–50%
- Oppositional disorder 35%
- Mood disorder 15–75%
- Anxiety disorder 25%
- Learning disability 10–92%

ADULT ADHD

Psychiatric Comorbidity

	Biederman N=120	Shekim N=56	Roy- Byrne N=46	Murphy & Barkley N=172
MDD	26%	10%	26%	18%
Dysthymia		25%	30%	32%
Alcohol	33%	39%	9%	35%
Drug	20%	30%	9%	14%
Panic	6%	15%	4%	32%
GAD	36%	53%		32%
Social phobia	32%			32%
Antisocial	16%			
Any diagnosis	77%	86%	56%	

ADULT ADHD: Does Diagnosis Depend On Mood Disorder Symptoms?

ADHD Patients With:	% Retaining Diagnosis*
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Major Depression (poor concentration)	57-86%
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Bipolar Illness (distractibility)	67-86%
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*When mood disorder symptoms are subtracted out

Milberger et al. 1995

ADULT ADHD AND ALCOHOLISM

Contributions to Cognitive Impairment

- 100 alcoholics and 80 controls
- Cognitive efficiency across domains measured
- ADHD measured by WURS and CBDC
- Cognitive impairment predicted by alcoholism diagnosis, not ADHD

Nixon et al., 1995

ADHD & SUBSTANCE ABUSE

- Risk for substance abuse not increased in ADHD children and teens (5-17 years old) (Biederman et al. 1997)
- Increased risk of substance abuse (drug not alcohol abuse) in ADHD adults (Biederman et al. 1995)
- Transition from teen to adult a vulnerable period for development of substance abuse in ADHD.

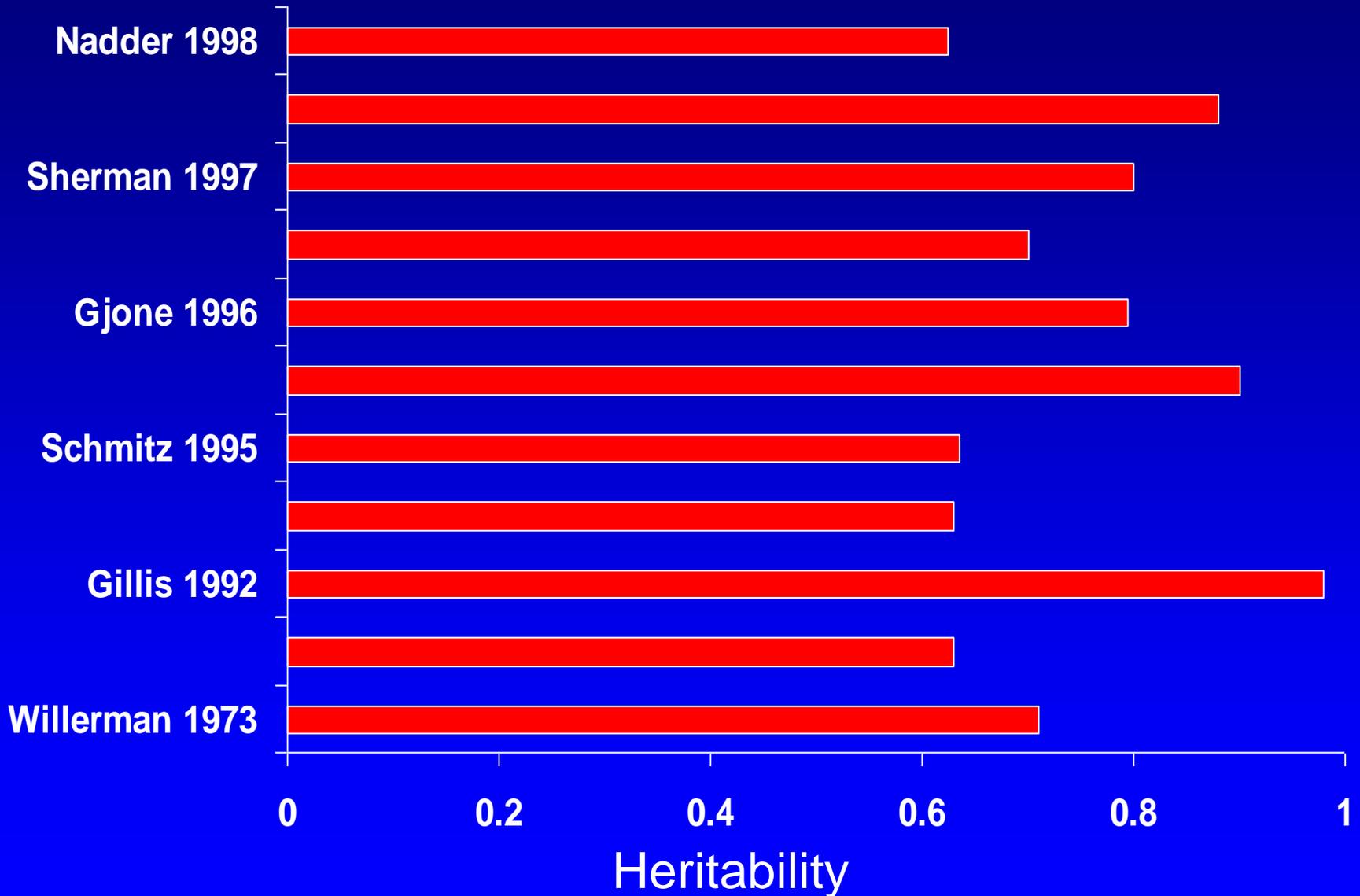
ADHD & SUBSTANCE ABUSE (continued...)

- Substance abuse in ADHD is more persistent (longer time required for remission) than uncomplicated substance abuse (Wilens et al., 1997)
- May be at higher risk for PTSD
 - 86% of ADD patients developing PTSD had Substance Abuse (Kunz et al., 1997)

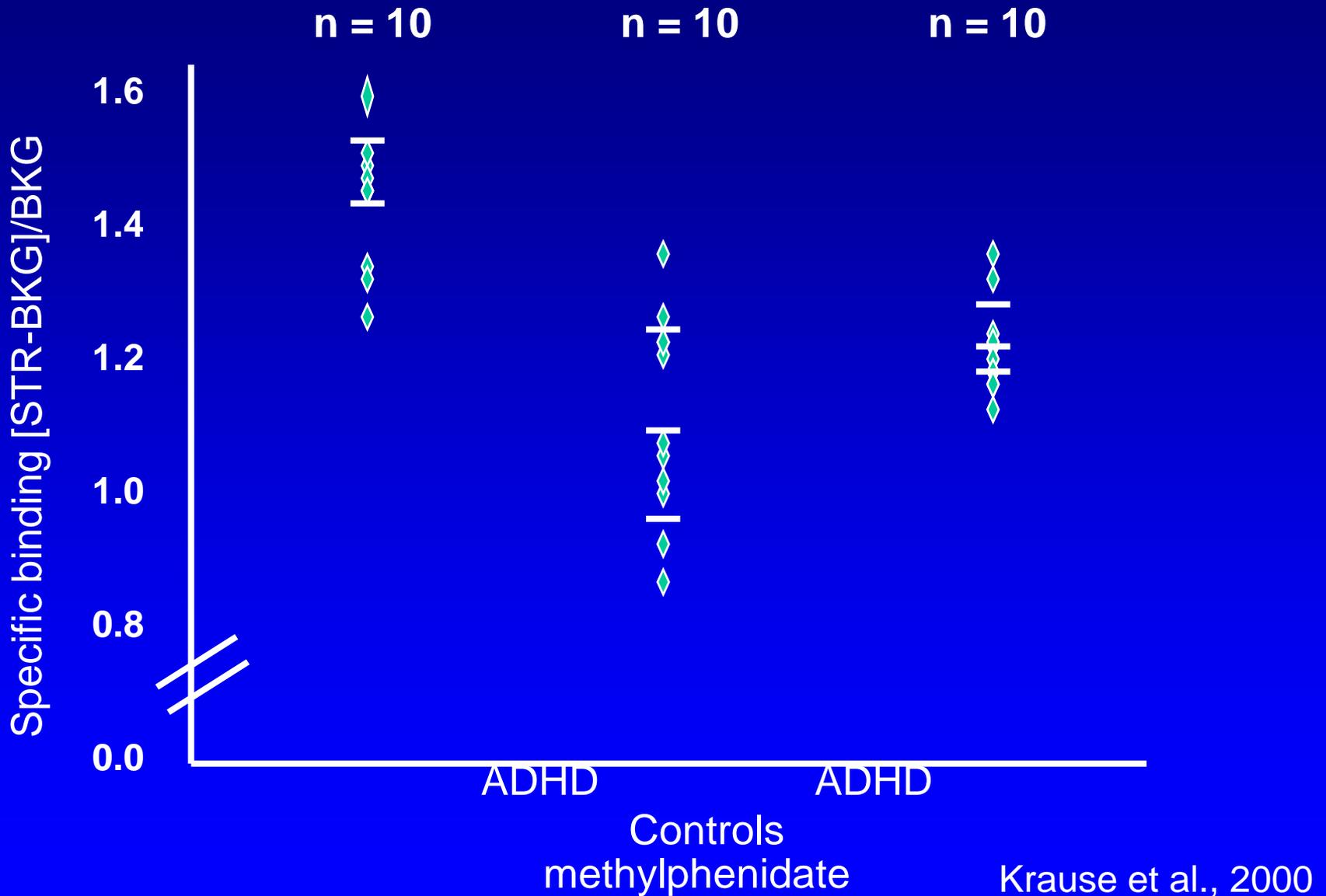
ADHD: GENETICS

- Monozygotic/Dizygotic Twin Concordance
50-90% vs 30% (Goodman & Stevenson 1989; Gillis et al. 1992; Sherman et al. 1997)
- Distinct Familial Subtypes?
 - ADHD-Bipolar (Faraone et al. 1997)
 - ADHD-Conduct (Faraone et al. 1991)
- Linkage with Dopamine D2, D4, transporter genes (Comings et al. 1991; Lahoste et al. 1996; Cook et al. 1995)
- ADHD Familiality strongest in persistent ADHD (i.e., adults) (Biederman et al. 1994)

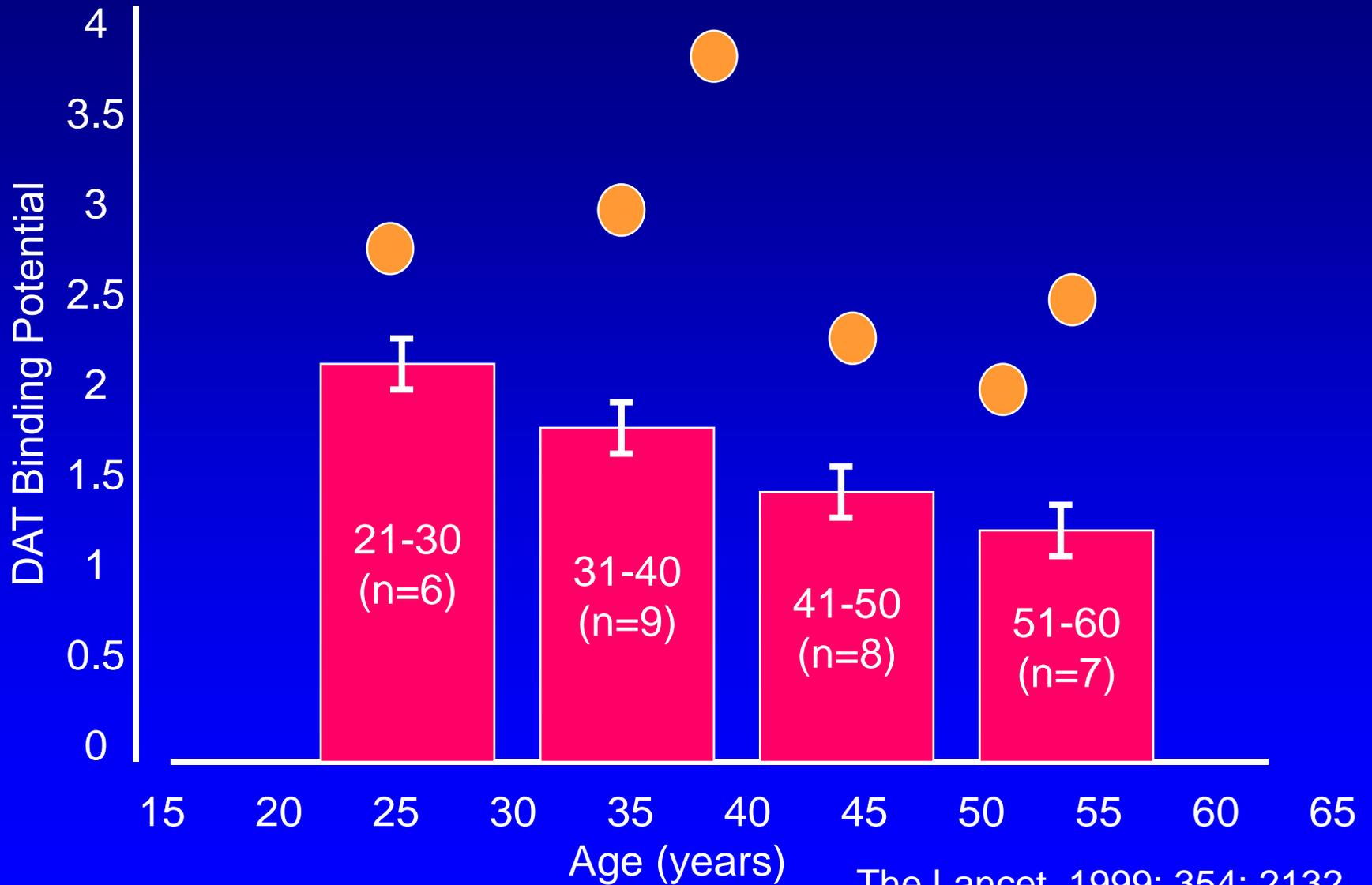
HERITABILITY OF ADHD



HIGH DAT IN ADULT ADHD: CORRECTION WITH METHYLPHENIDATE



DAT IN ADHD ADULTS



The Lancet, 1999; 354: 2132

NON-GENETIC CAUSES OF ADHD

- Frontal Lobe Injury
- Malnutrition
- Lead Poisoning
- Fetal Alcohol Syndrome
- Perinatal bleeding, stress, smoking, drugs

(Popper 1997; Milberger et al. 1997)

ADHD & CIGARETTE SMOKING

FAMILIAL ADHD IS A RISK FACTOR FOR SMOKING

ADHD Siblings	17%
with ADHD	25%
without ADHD	16%
Non-ADHD Siblings	7%

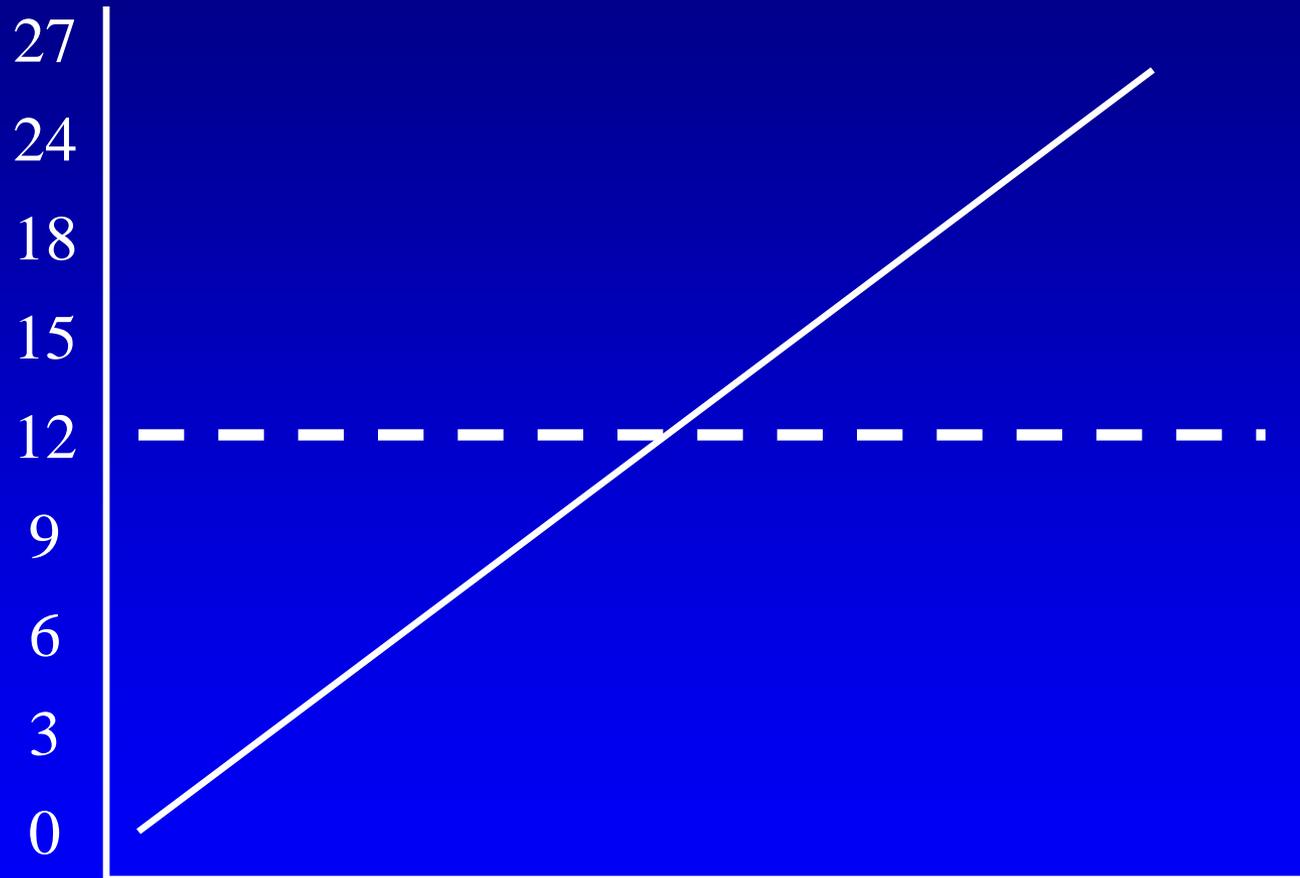
MATERNAL SMOKING IS A RISK FACTOR FOR ADHD

ADHD	22%
Controls	8%

Milberger et al. 1996; 1997

ADHD IS A
CLINICAL
DIAGNOSIS

ADHD: A CONTINUUM



Possible Score On Harborview ADHD DSM-IV Scale
(9 items rated 0-3; Need 6 rated 2 or 3)

ADULT ADHD

Diagnostic Mimics

- Substance abuse
 - Alcohol
 - Marijuana
- Major depression
- Bipolar illness
- Social phobia
- Low IQ
- Obsessive-compulsive personality
- Learning disability ?
 - Particularly verbal

ADULT ADHD

Keys to Diagnosis

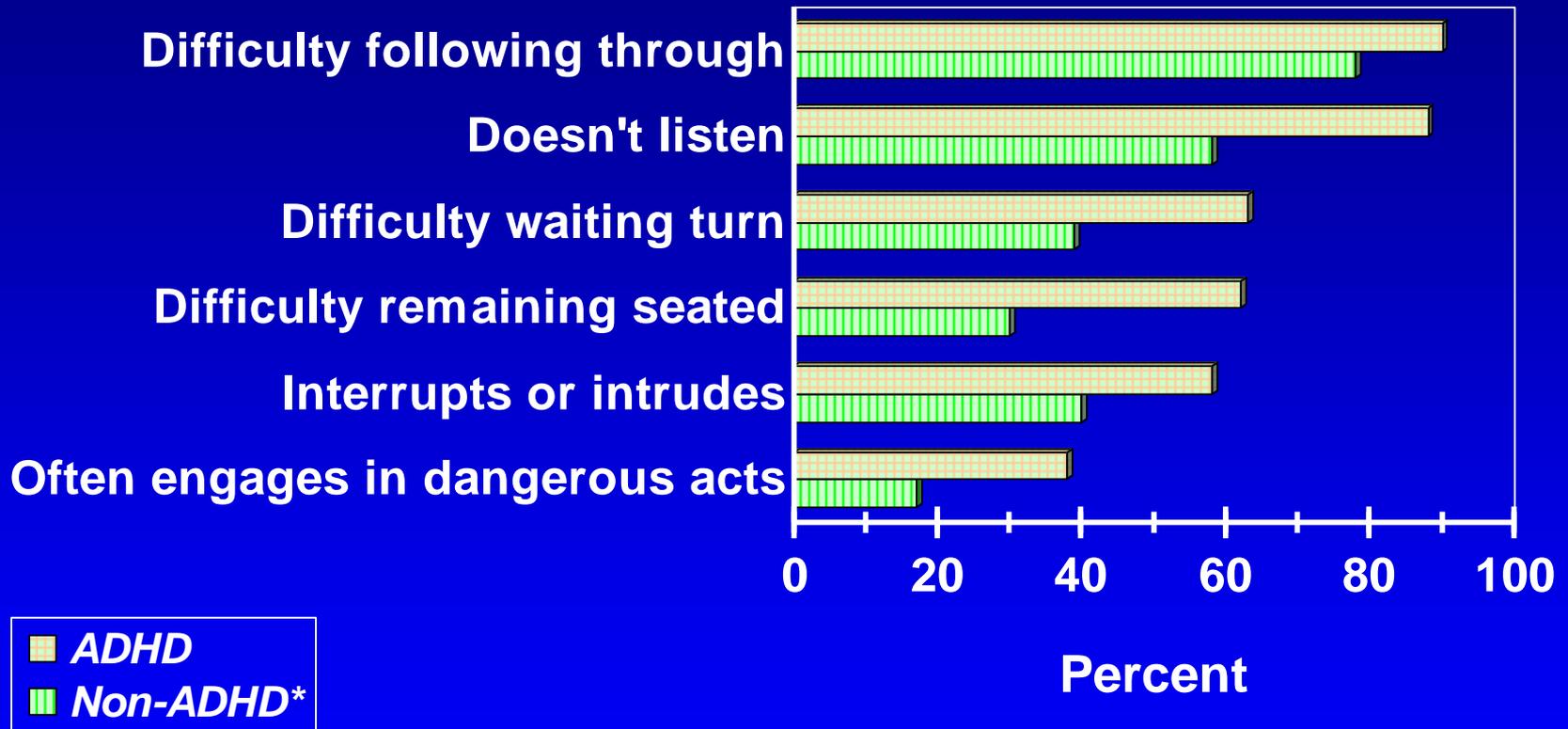
- Childhood history
- Corroboration by outside source
- Proof of impairment
- Persistence without fluctuation
- Effect of context
- Cognitive testing
- Questionnaires

ADHD-SPECIFIC ITEMS

ADHD Adults vs Non-ADHD Parents of ADHD Children

- More marriages
- More speeding tickets
- More MVAs
- License suspended
- More jobs
- Impulsively quit jobs
- Fired from jobs
- Increased SCL-90?
- Use and abuse of illegal drugs
- Below average grades
- Suspended from school
- Dropped out of college

ADHD-SPECIFIC SYMPTOMS



*Non-ADHD = Non-ADHD parents of children who have ADHD

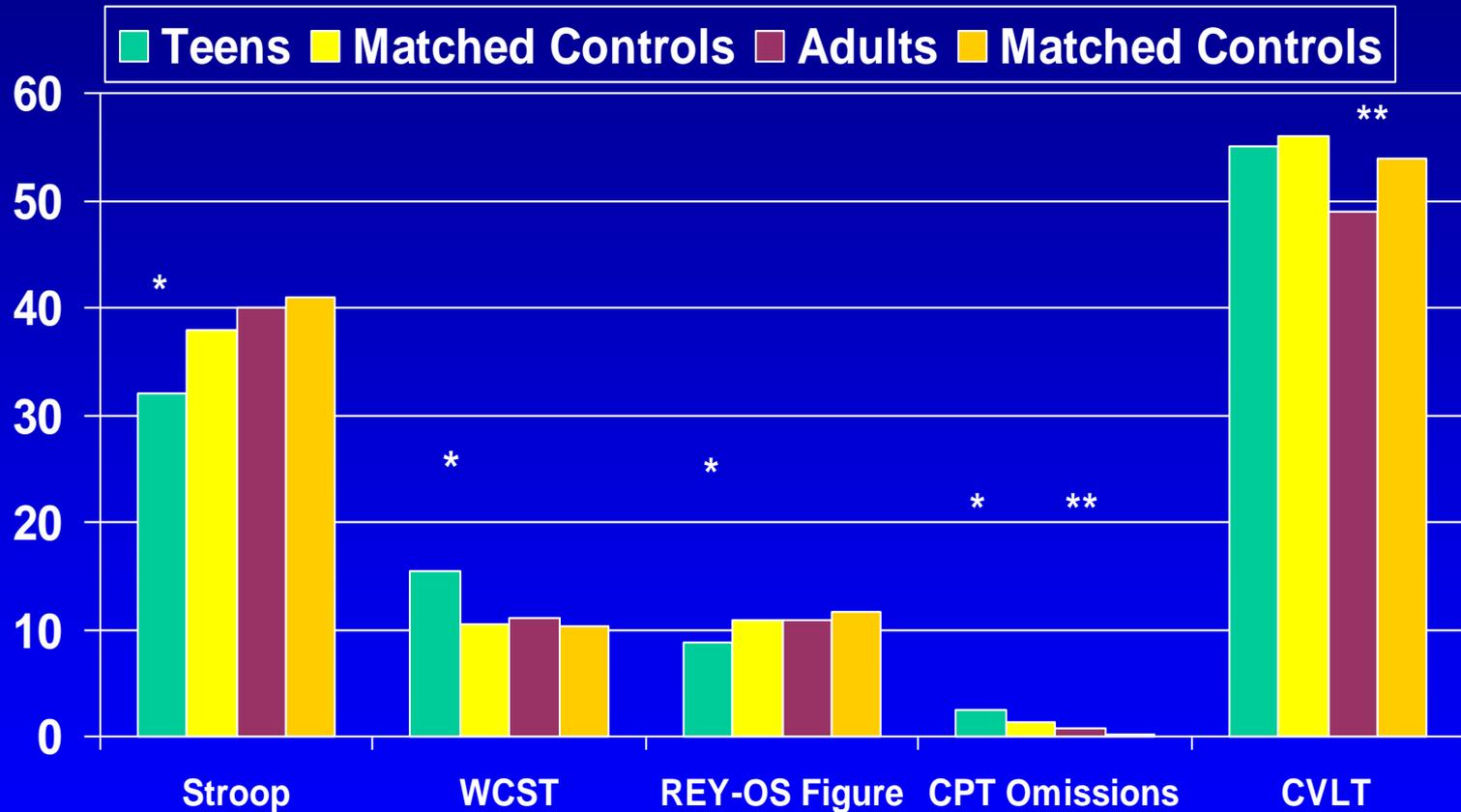
ADULT ADHD: ASSESSMENT INSTRUMENTS

- Self-Report Indices of ADHD:
 - Wender-Utah Rating Scale (WURS)
 - Triolo and Murphy Attention-Deficit Scales for Adults (ADSA)
 - Barkley Current Symptoms Scale - Self Report
 - Harborview ADHD - DSM-IV Scale
 - Weyandt Adult Rating Scale (ARS)

ADULT ADHD: ASSESSMENT INSTRUMENTS

- Cognitive Testing:
 - CPT, Stroop, CVLT, WCST
(Measures of Attention, Working Memory, and Execution Functions)
 - WAIS - Vocabulary and Block Design
(Estimate of Full Scale IQ)
 - WAIS Freedom from Distractibility
(Arithmetic, Digit Span, Digit Symbol)
 - WRAT 3 -- Academic Achievement

ADHD: NEUROPSYCH TESTING



Seidman et al. 1997; 1998

* Teens vs Controls

** Adults vs Controls

ADULT ADHD

“Hit Rate” in a Specialty Clinic

Referred by Self, Clinician, or Relative with High Suspicion of ADHD (n=143)

	ADHD Dx N=46	ADHD Features N=51	No ADHD N=56
Age	33.1	36.3	39.5*
Education	13.1	14.2	15*
Hyperactivity	63%*	37%	15%
Informant	44%*	25%	15%
Current substance abuse	8%	25%*	6%
Drinks/week	3.9±5.5	4.1±5.2	1.5±2.6*
LD	37%*	15%	13%
WRAT-reading	97%*	106	107
CPT index	6.7±6.0	7.6±6.1	4.8±5.1
WURS	56±20	51±22	38±24*
ADHD by WURS	71%	60%	39%*

*All differences significant at p<0.05

ADULT ADHD: Methods of Corroboration

- History
 - Parent Phone Interviews
 - Report Cards, Teachers' Comments, Other Evaluations (e.g., work)
 - Behavioral Markers (Repeat Grade--33% vs 8%, Cs&Ds--"most", Special Ed)
- Current
 - Significant Other
 - Employer
 - Behavioral Markers (Divorces, Multiple Jobs, Switching Set Within Job, Lists without Doing, Speeding, MVA, Avoidance of Meetings, Compensation with Assistants or Spouse)

ADHD AND LEARNING DISORDERS

Convergent Concepts?

- Both ADHD and LD are operationally defined
 - ADHD behaviors
 - Gap between achievement and IQ
- Both ADHD and LD are thought to be driven by underlying cognitive/ neurophysiologic abnormalities which are not used to define or diagnose
- The information-processing deficits in LD are more proximal (sensory, cognitive) to those of ADHD (motor preparedness, intention)

ADHD AND LEARNING DISORDERS

Convergent Concepts?

- ADHD patients have encoding deficits that may appear sensory but are due to deficient strategies needed for encoding
 - These may only appear later with increased demands
- LD patients may show “pseudo-ADHD” if rules needed for role-governed behavior don’t get processed due to language deficits
- As individuals mature, both ADHD and LD look more LD-like
 - ADHD loses impulsivity
 - LD rehearses rules better so behavior more role-governed

ADULT ADHD

Treatment Approaches

- Pharmacotherapy
 - Stimulants
 - Methylphenidate
 - Dextroamphetamine
 - Pemoline
 - Antidepressants
 - Tricyclics (desipramine)
 - Bupropion
 - Venlafaxine
 - ? Antihypertensives
- Psychoeducational

ADULT ADHD: STIMULANTS

- Only 10 studies (100 studies in children)
- Response in most about 50% (70% in children)
- But best study had 78% response rate using higher dose (1mg/kg)
Methylphenidate

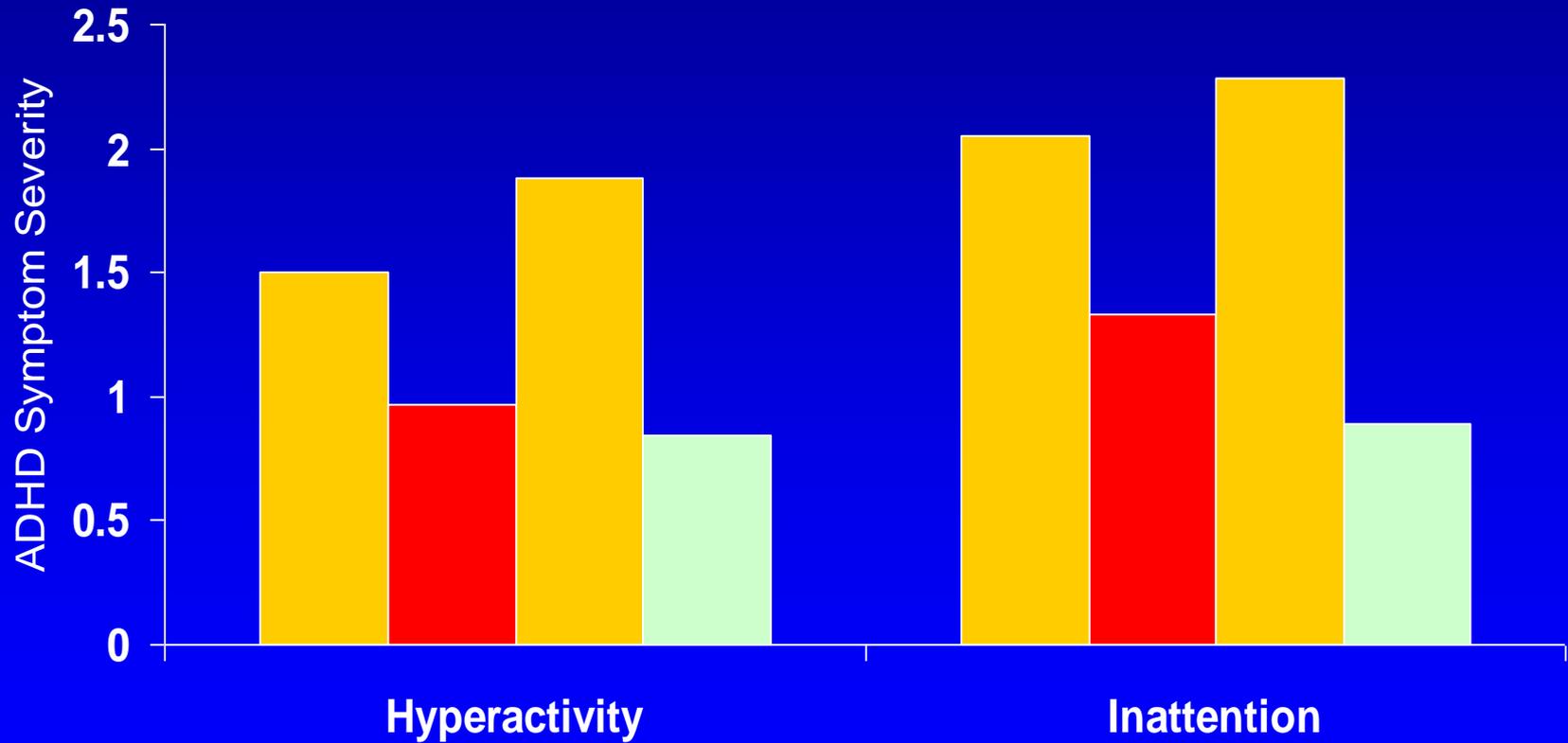
ADULT ADHD: STIMULANTS

(cont'd)

- Not enough data to show comorbidity effects (in children, poorer cognitive response with comorbid anxiety; poorer behavioral response with comorbid depression)
- Side effects: Insomnia, edgy, anorexia, dysphoria, headaches (not psychosis or abuse)
- Methylphenidate 5 mg TID-QID, ↑ by 5 mg/dose/week
- Dextroamphetamine 2.5 mg TID, ↑ by 2-5 mg/dose/ week
- Pemoline 37.5 mg QAM, 75 mg QAM week 2, ↑ to 150 mg if needed

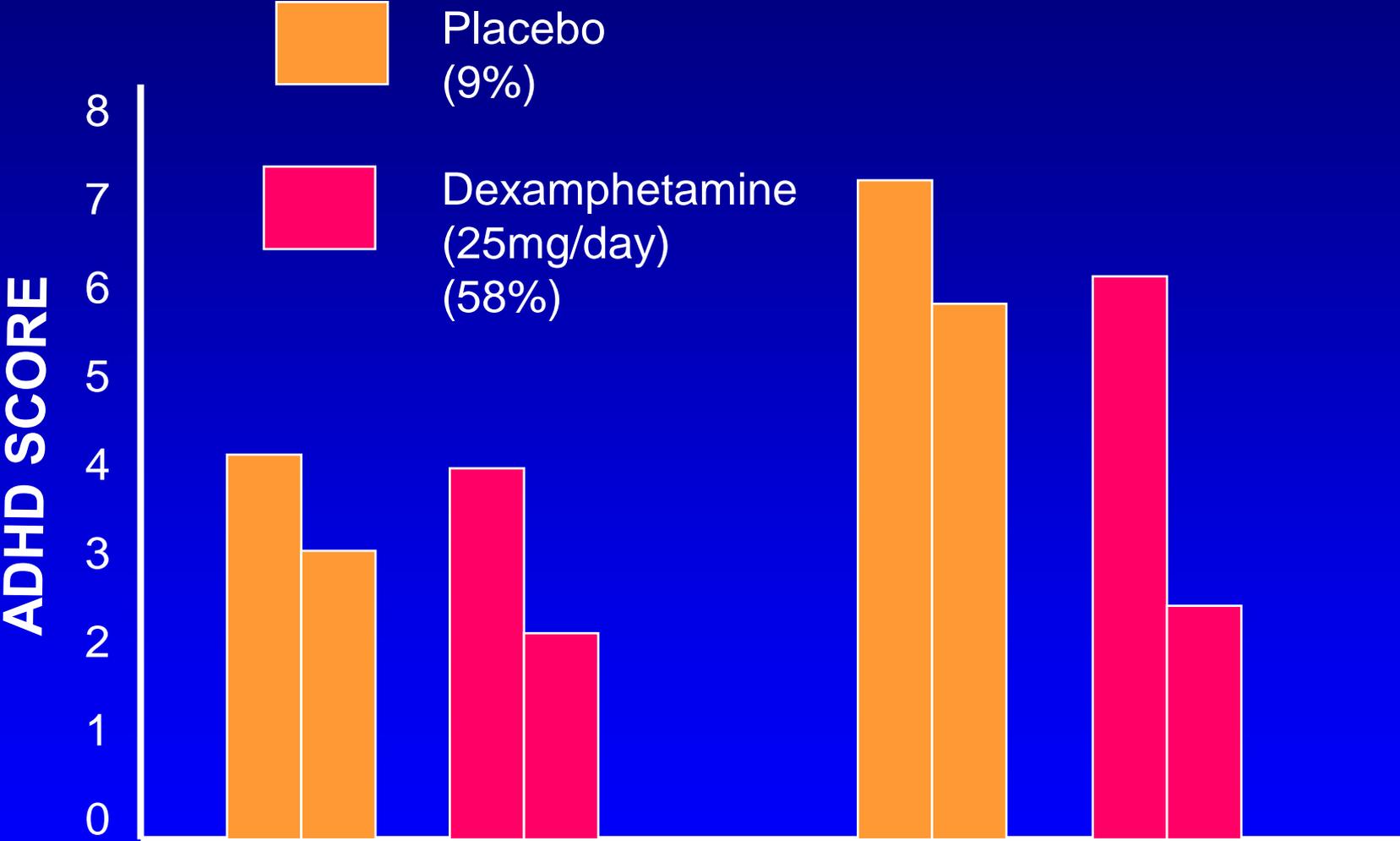
STIMULANTS IN ADULT ADHD: METHYLPHENIDATE VS AMPHETAMINE SALTS

■ Placebo (47%) ■ Amphetamine Salts (0.4mg/kg)(70%) ■ Methylphenidate (1mg/kg)(78%)



Spencer et al., 1995; 2001

DEXAMPHETAMINE VS PLACEBO IN ADULT ADHD



Hyperactivity

Inattention

Patterson et al.,
1999

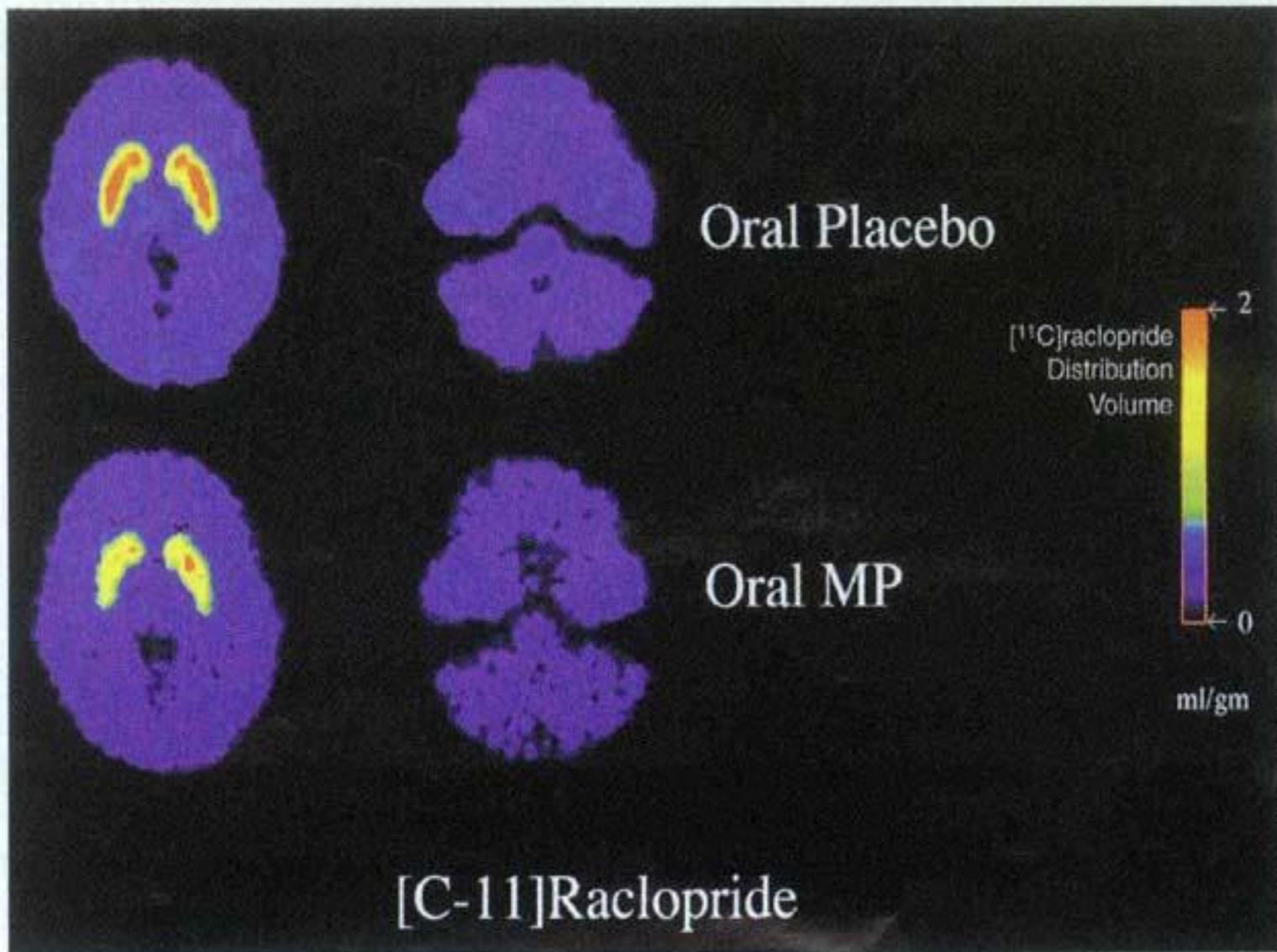
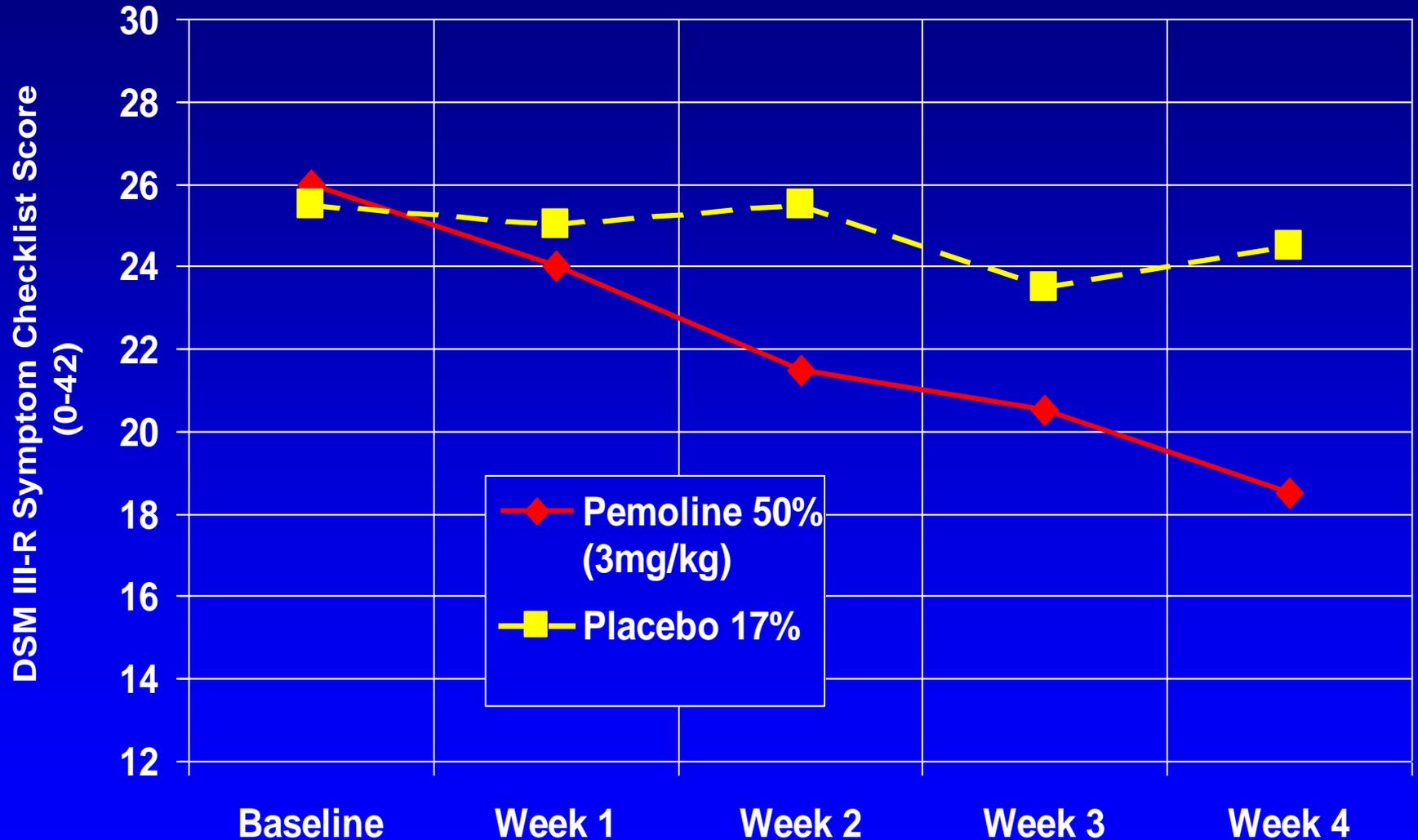


Image courtesy of Brookhaven National Laboratory

PET scan images, taken at the level of the striatum (left) and the cerebellum (right) of a radiotracer specific to dopamine D2 receptors, show reduced binding of the tracer in the striatum after administration of 60 mg of oral methylphenidate (bottom) compared with placebo (top).

PEMOLINE FOR ADULT ADHD



ADULT ADHD

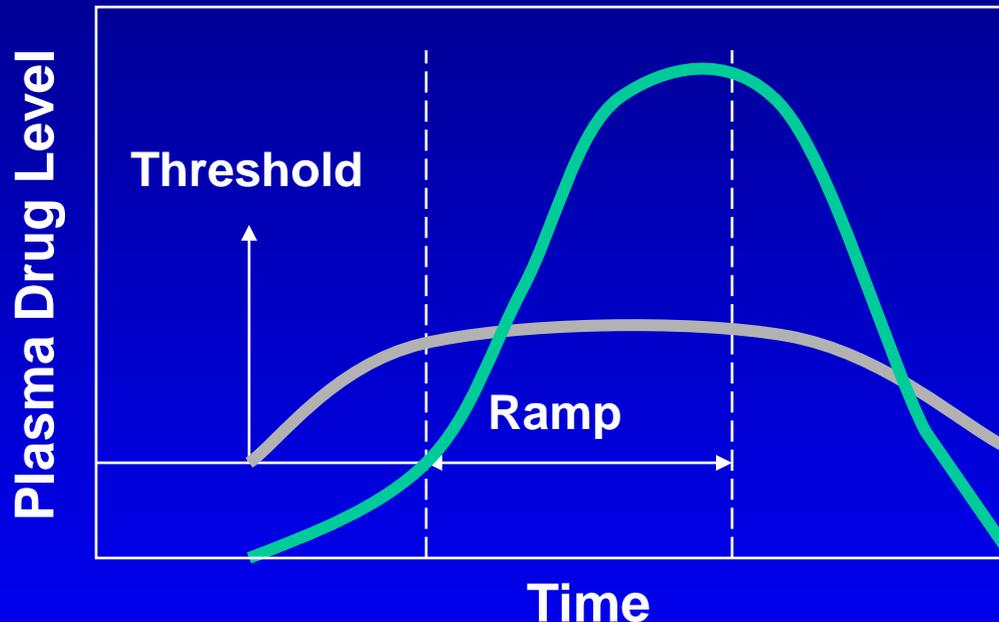
Stimulant Pharmacokinetics

Medication	Tablet Size & Preparation (mg)		Half-Life (hr)	Dosing (qday)	Dose Range (qday)
	Short-Acting	Long-Acting			
Methylphenidate (Ritalin-Ciba)	5, 10, 20	20 SR	2-3 (reg) 2-6 (SR)	1-5x	0.1-2.0mg/kg (10-140mg)
Dextroamphetamine (Dexedrine-SK&F)	5	5, 10, 15 (spansule)	3-6	1-5x	0.1-1.0 mg/kg (5-70 mg)
Pemoline (Cylert-Abbott)		18, 75, 37.5, 75	11-13	1-2x	0.5-3.0 mg/kg (37.5-21.5 mg)

SR=Sustained Release

RAMP vs THRESHOLD STIMULANTS

Duration of Effect in Relation to Absorption and Elimination



- Pemoline exerts activity into post-distribution phase once “threshold” dose is administered, while methylphenidate and dextroamphetamine are active only during the “ramp” of the absorption phase

Source: Floyd R. Sallee, MD, PhD

ASPECTS OF STIMULANT EFFECTS IN ADHD

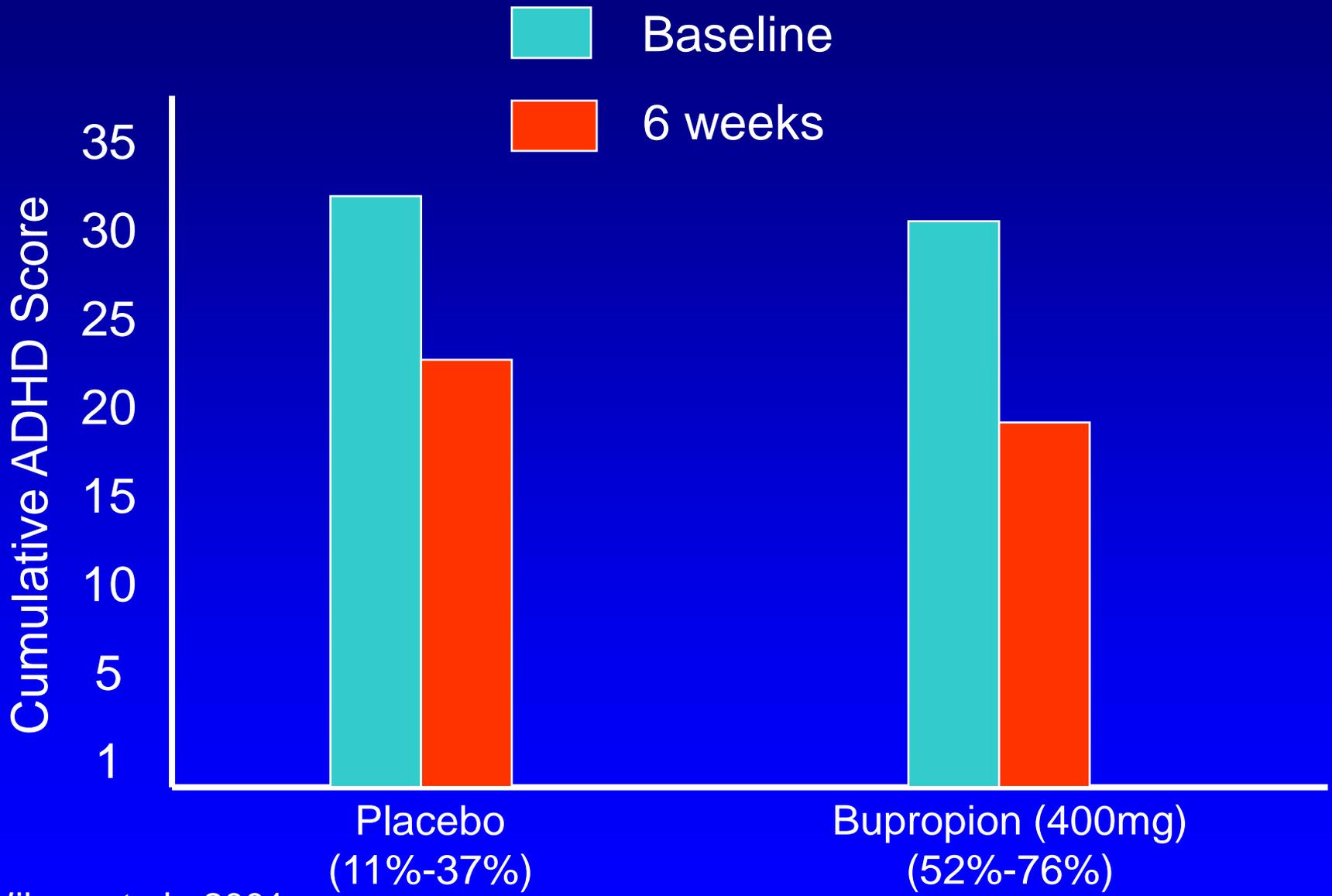
- Favorable response is not diagnostic (Rapaport 1978)
- Effect Size on IQ/achievement (.35) less than half that on behavior and attention (.83) (Swanson et al. 1993)
- Stimulants increase the reward value of reinforcers (amotivational aspects of depressions?) (Wilkeson et al. 1995)
- Stimulants are antidepressants in some patients (Stoll et al. 1996)

ADULT ADHD

Antidepressants

- Tricyclics
 - 183 mg DMI 17/25 (68%) respond; 97 mg NT 5/12 (42%) respond (Wilens et al., 1995)
 - DMI (2.5 mg/kg) 68% respond vs 0% placebo (Wilens et al.)
- Bupropion
 - 360 mg; 5/14 (36%) dropouts; 9/14 (64%) respond (Wender & Reimherr)
- Venlafaxine
 - 96 mg; 7/18 (39%) dropouts; 8/11 (73%) respond (Hedges et al.)
 - 110 mg; 4/16 (25%) dropouts; 10/12 (83%) respond (Adler et al.)
- SSRIs
 - No data
 - Anecdotal single reports

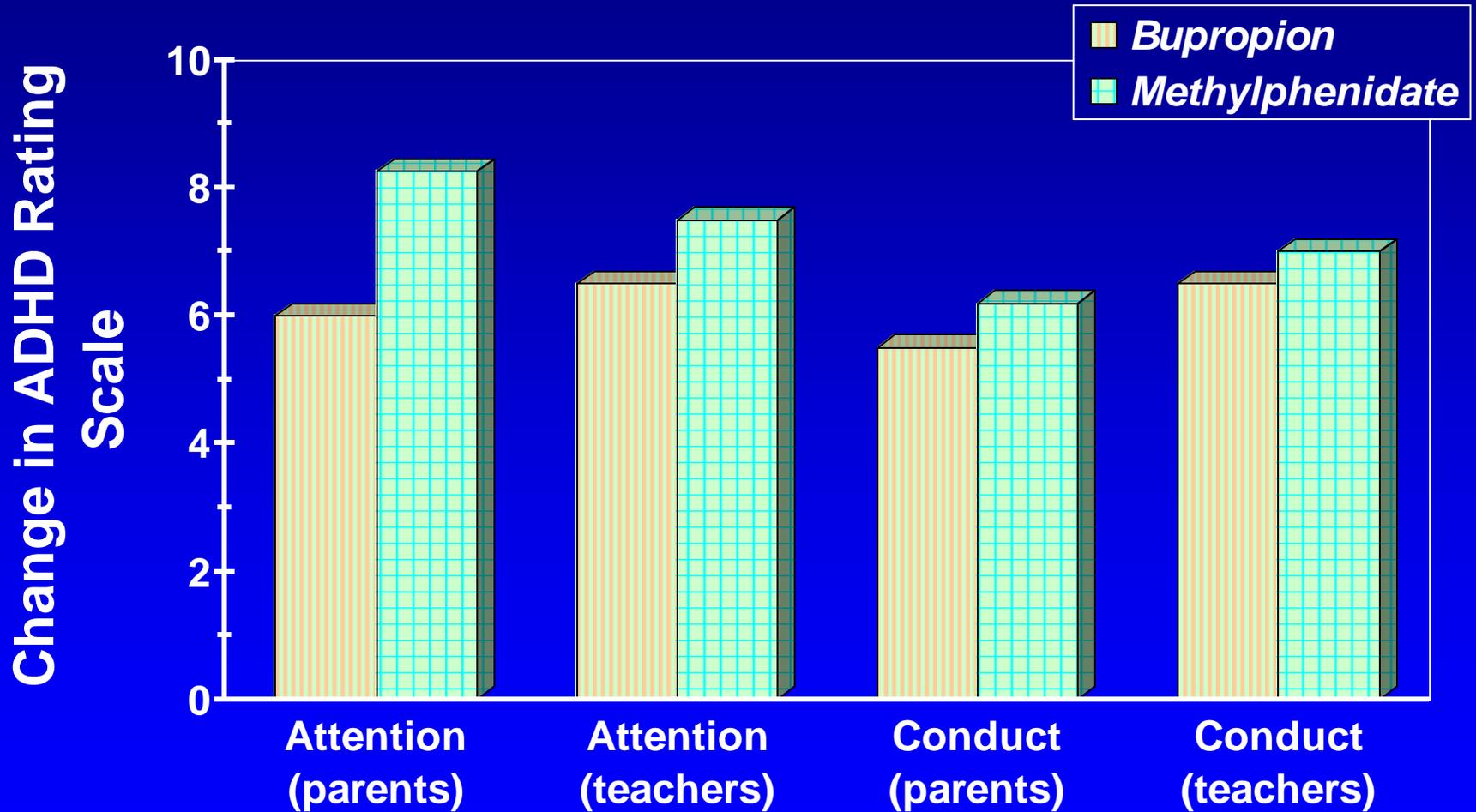
BUPROPION VS PLACEBO IN ADULT ADHD



Wilens et al., 2001

ADOLESCENT ADHD

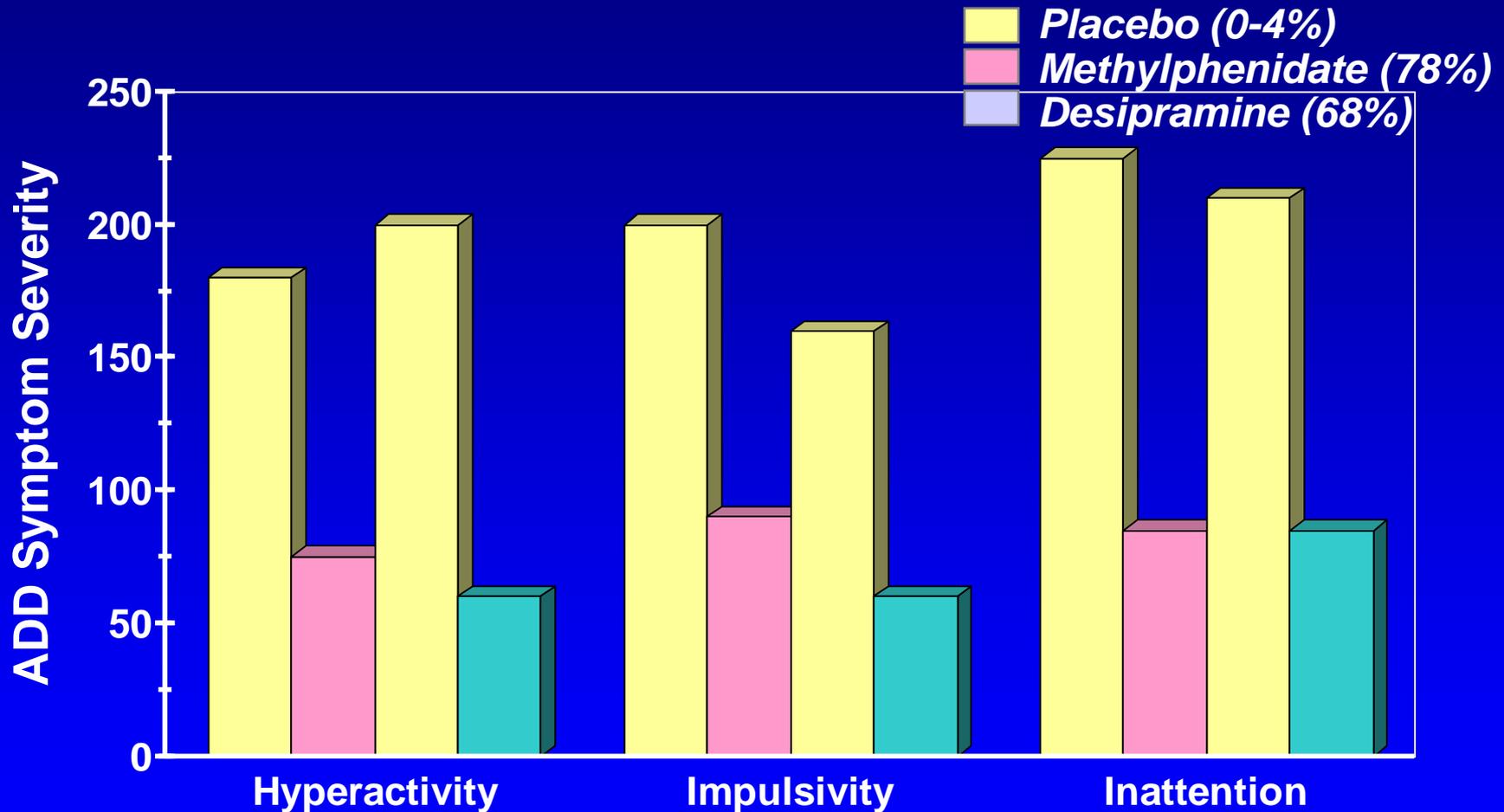
Bupropion vs Methylphenidate



Barrickman et al., 1995

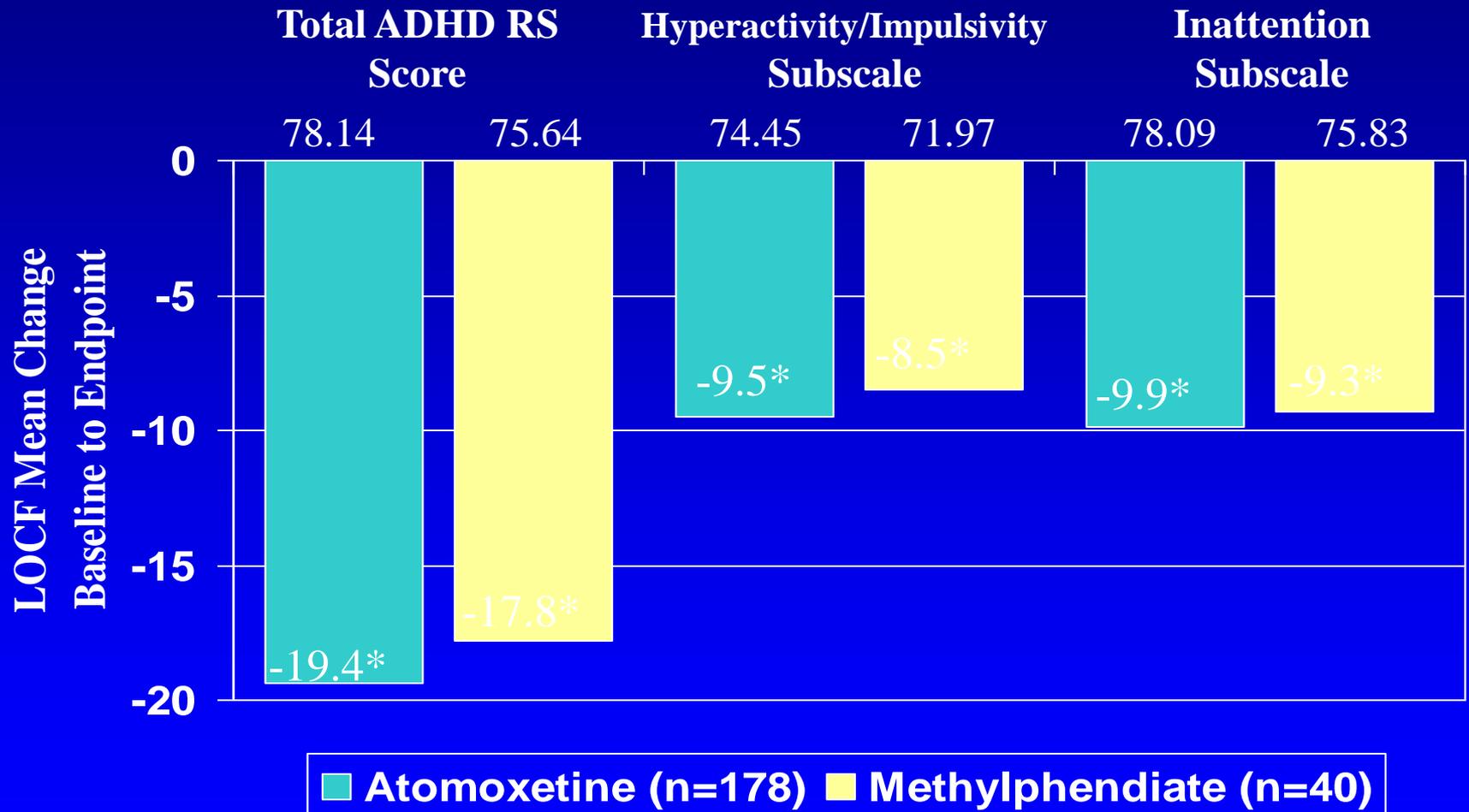
ADOLESCENT ADHD

Desipramine vs Methylphenidate



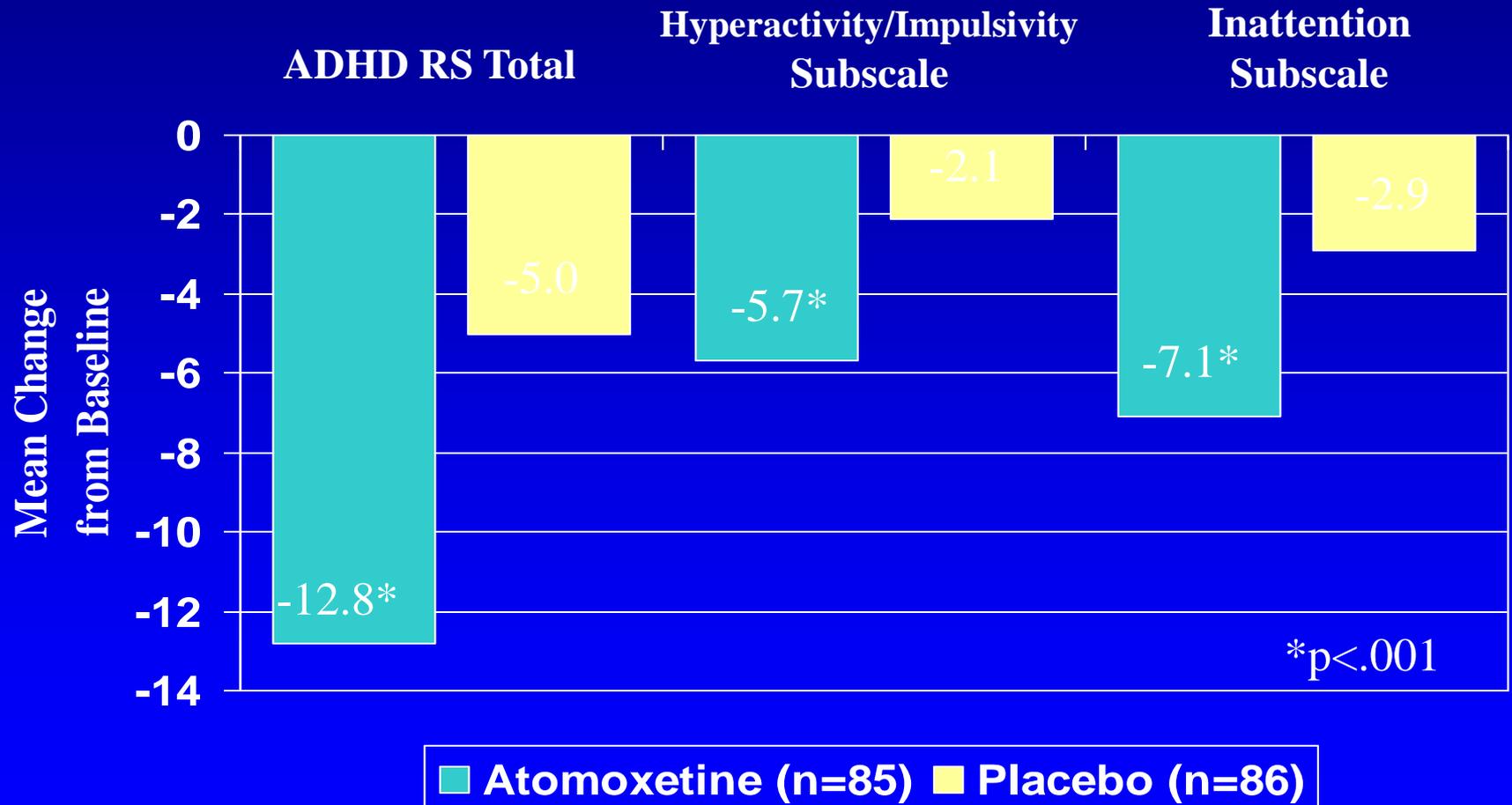
Spencer et al.
Wilens et al.

Open Label Randomized Trial of Atomoxetine & Methylphenidate in Children with ADHD



*p<.001 within treatment group, baseline to endpoint. p=NS between groups.

Once Daily Dosing: Improvement in Core Symptoms in Children with ADHD

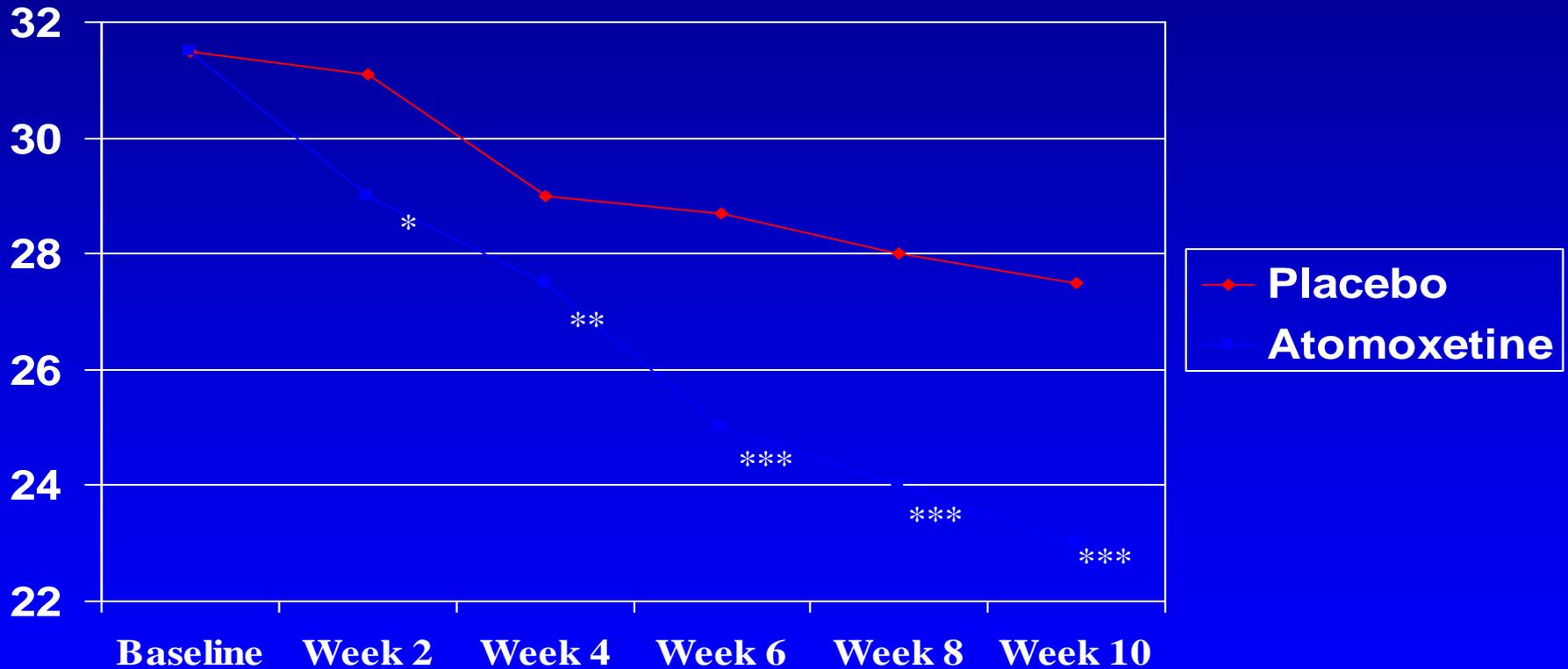


Tolerability in Combined Child/Adolescent Studies

Event*	Atomoxetine (n=425) %	Placebo (n=292) %	P-Value
Low Appetite	14.1	5.8	<.001
Dizziness	6.1	2.4	.019
Dyspepsia	4.5	1.4	.029
Dermatitis	4.5	1.7	NS
Constipation	2.4	1.0	NS
Mood swings	2.4	0.7	NS
Influenza	2.1	1.0	NS

- No evidence of symptom rebound or withdrawal syndrome noted
 - Events reported in the QD trials but not in the BID trials include: vomiting, nausea, dyspepsia, and fatigue (p<.05 vs placebo)
- * Events reported by at least 2% of patients treated with Atomoxetine, and at least twice placebo in registration studies. The following events were reported by at least 2% of patients treated with Atomoxetine and equal to or less than placebo: arthraigia, gastroenteritis, viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

EFFICACY IN ADULTS

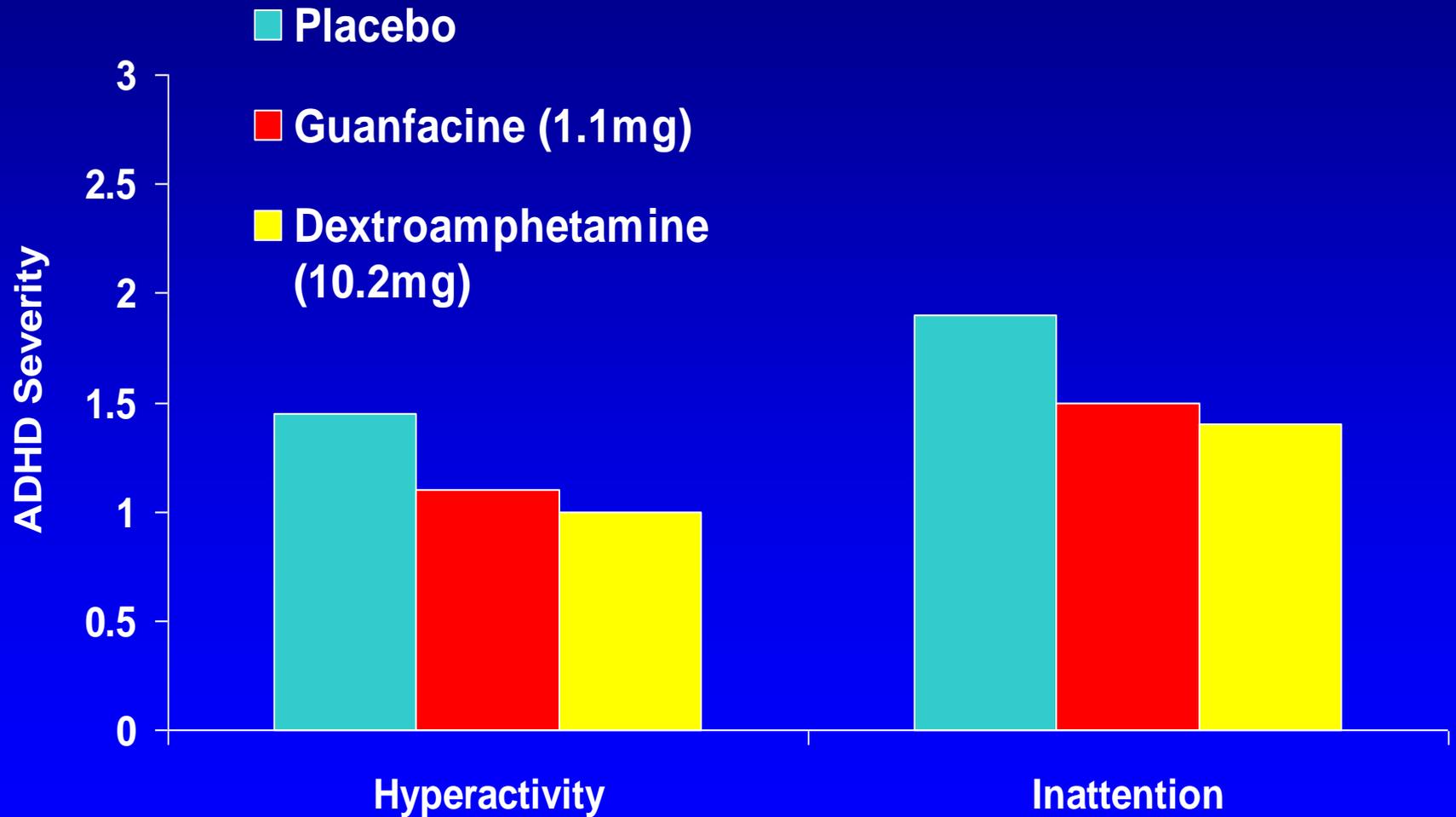


*p<.003 **p<.05 ***p<=.001

Treatment-Emergent Adverse Events Reported in $\geq 10\%$ in Either Group

	Atomoxetine N=184	Methylphenidate N=40	P-Value Fisher's exact
Headache	31.0%	32.5%	.852
Abdominal pain	23.4%	17.5%	.531
Anorexia	19.0%	15.0%	.656
Rhinitis	17.9%	20.0%	.822
Nervousness	15.8%	10.0%	.464
Vomiting	12.0%	0	.017
Fever	10.9%	10.0%	1.000
Somnolence	10.9%	0	.029
Nausea	10.3%	5.0%	.383
Insomnia	9.2%	17.5%	.155
Accidental injury	5.4%	12.5%	.153
Flu syndrome	4.9%	10.0%	.256

GUANFACINE VS DEXTROAMPHETAMINE IN ADULT ADHD



CARBAMAZEPINE IN ADHD CHILDREN

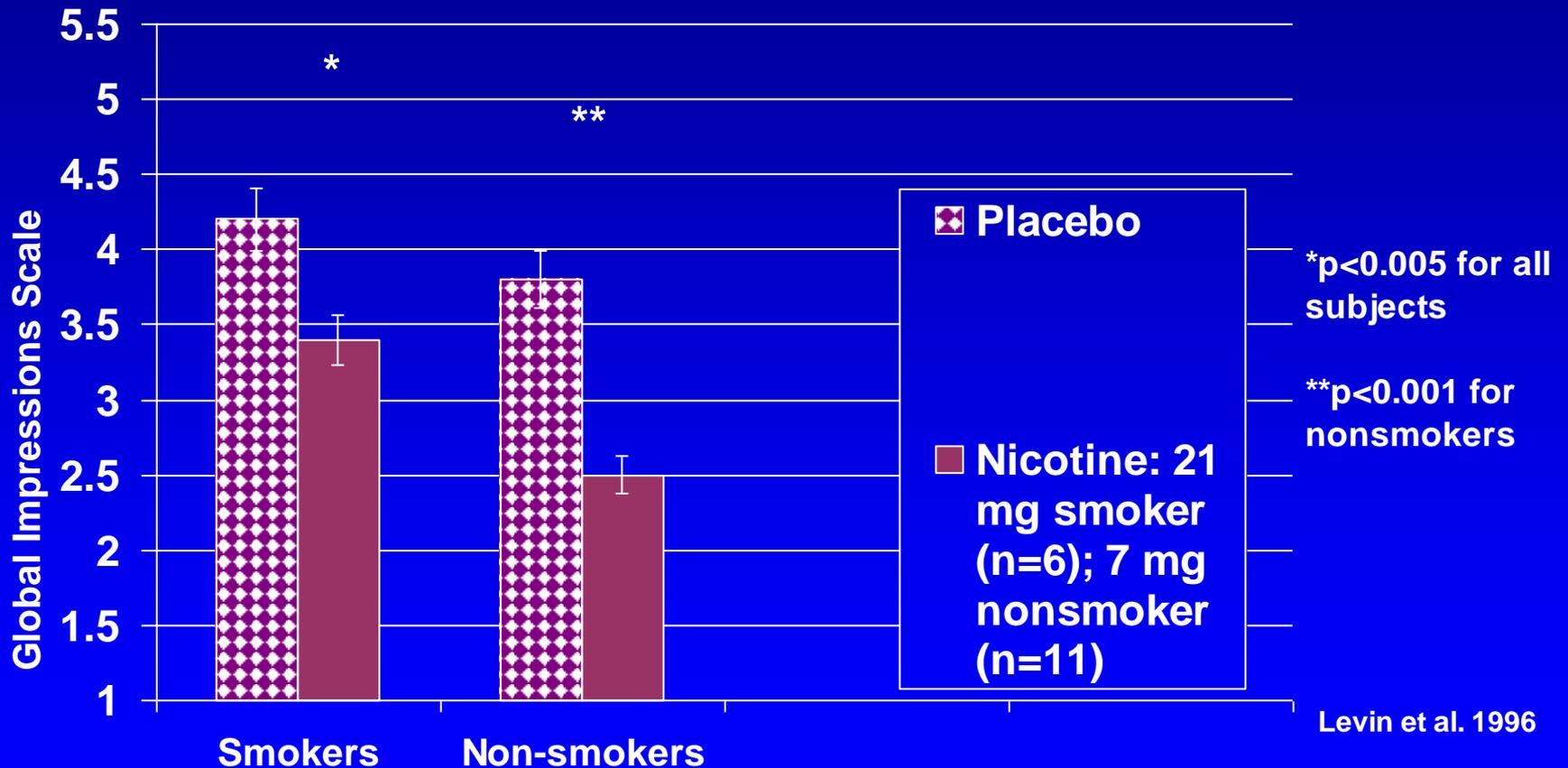
- 3 placebo controlled studies (1 parallel n=16; 2 crossover n=94 total)
- Daily doses 200-600 mg
- 39/110 (35%) abnormal EEGs; 103/110 (94%) normal IQ
- 32/57 (56%) CBZ vs 8/53 (15%) PL marked change

Garcia Belmonte & Pirgliese 1970

Groh 1971

Puente et al. 1973

NICOTINE PATCH: ACUTE EFFECT ON ADHD



METHYLPHENIDATE IN ADHD ADULTS WITH COCAINE ABUSE

- 12 entered, 10 completed 8 wks, 8 completed 12 wks
- Significant reductions in inattention, hyperactivity, over-reactivity, disorganization & impulsivity at 8 wks on TADDS (modeled after WURS)
- Significant reduction in days cocaine use/month (9.8+2.7 to 1.1+0.5 $p < .006$)
- Significant reduction in % 3x weekly cocaine positive urines from 8/10 positive to 3/10 positive

ADULT ADHD: GOALS FOR PSYCHOTHERAPY

- PSYCHOEDUCATION
 - Use of medications
 - Symptom recognition
- BEHAVIORAL SELF-MANAGEMENT SKILLS
 - Goal setting
 - Problem solving skills
- COGNITIVE BEHAVIOR THERAPY to address low self-esteem and related sequelae of ADHD.

CONCLUSIONS

- ADHD in adults, previously unrecognized by clinicians, is now often considered as one cause of social, academic, and occupational impairment
- Estimates of the prevalence of adult ADHD vary considerably and likely depend on whether a more narrow or broader, more inclusive, definition is used
- Extensive psychiatric comorbidity and poor recall of childhood behavior in adult ADHD can make accurate diagnosis difficult

CONCLUSIONS

- Psychostimulants and noradrenergic antidepressants are the two major medications of choice. Stimulants are somewhat more effective, but antidepressants may be preferable in patients with comorbid mood, anxiety, or substance abuse disorders.
- Psychoeducational and cognitive-behavioral interventions are likely important adjuncts, but there are little data supporting the value of particular interventions or techniques in adults.