

Depression in Children and Adolescents

Karen Dineen Wagner, MD, PhD

Marie B. Gale Centennial Professor & Vice Chair

Department of Psychiatry & Behavioral Sciences

Director, Division of Child & Adolescent Psychiatry

University of Texas Medical Branch

Galveston, Texas

Disclosures (Past 12 Months)

- Dr Wagner has received honoraria from UBM Medica, American Psychiatric Association, Slack Inc, Las Vegas Psychiatric Society, Partners Healthcare, Brain and Behavior Research Foundation, NAC CME, University of Wisconsin. She has been a consultant for Lundbeck (no financial compensation).

Off-Label Use - Depression

Medications discussed in this presentation are off-label for the acute and maintenance treatment of major depression in children and adolescents, with the exception of fluoxetine (ages 8 to 18) and escitalopram (ages 12 to 17).

Lifetime Prevalence of Adolescent Depression

- National Comorbidity Survey–Adolescent Supplement
- Face-to-face study of 10,123 US adolescents, ages 13 to 18 years
- Modified version of World Health Organization Composite International Diagnostic Interview

	Sex		Age			Total	Severe Impairment
	Female %	Male %	13-14	15-16	17-18		%
MDD or Dysthymia	15.9	7.7	8.4	12.6	15.4	11.7	8.7

Diagnosis of Major Depression in Children and Adolescents

- DSM IV criteria
 - Depressed or irritable mood
 - Diminished interest in activities
 - Appetite or weight changes
 - Sleep disturbance
 - Psychomotor agitation or retardation

Diagnosis of Major Depression in Children and Adolescents

- DSM IV criteria
 - Fatigue or loss of energy
 - Worthlessness or guilt
 - Diminished concentration or indecisiveness
 - Suicidal ideation, attempt, or plan

Comorbid Disorders Associated with Major Depression in Children and Adolescents

- Anxiety disorders
- Attention-deficit hyperactivity disorder
- Conduct disorder
- Substance abuse
- Anorexia nervosa, bulimia

Course of Depression in Youth

- Mean duration of episode of depression
 - 17 months
- Recovery rate
 - 85% (over a 5-year period)
- Recurrence of depression
 - 40%

Early Onset Depression and Suicidality

	Preadult (<18 y) onset (n=132)*	Adult (≥18 y) onset (n=143)*
Mean current age	39	47
Number of suicide attempts	50	23
Duration of depression, y	26	19
Number of MDD episodes	6	5

*All significant differences

Williams JMG et al. *J Affective Disorders*. 2012;138:173-179.

Early Onset Depression and Substance Use

- Prospective longitudinal study of 1,545 adolescent twins assessed at age 14 years and at 17.5 years

Early Onset Depressive Disorders (age 14 y)	Odds Ratio (at 17.5 y)
Daily smoking	2.3
Frequent (>20 times) drug use	4.7
Frequent (>2 days/wk) alcohol use	2.0
Recurrent intoxication	1.8

Adulthood Outcomes of Child and Adolescent Depression

- 113 youths with major depression
- Follow-up 8 years (mean)
- Findings
 - More than half (56%) had subsequent depression
 - 18% remained persistently depressed

FDA Approval for **Acute** Treatment of Major Depressive Disorder

<u>Medication</u>	<u>Ages</u>
Fluoxetine	8-17
Escitalopram	12-17

Controlled Pediatric Depression Trials

	Medication	Ages	Number of Studies
Positive* Studies	Citalopram	7-17	1
	Sertraline	6-17	2 (a priori pooled analysis)**
Negative* Studies	Citalopram	13-18	1
	Escitalopram	6-17	1
	Mirtazapine	7-18 7-18	2
	Nefazadone	7-17 12-17	2
	Paroxetine	7-17 12-18 13-18	3
	Venlafaxine	7-17 7-17	2

* On primary outcome measure

**Individual trials negative

(Emslie et al, 2002; 1997; 2008; March et al, 2004; Wagner et al, 2003; 2004 Berard et al, 2006; Keller et al, 2001; Emslie et al, 2006; 2007; Wagner et al, 2006; Rynn et al, 2002; Von Knorring et al, 2006; Rynn et al, 2002; www.fda.gov/cder/foi/esum/2004/20152s032_serzone)

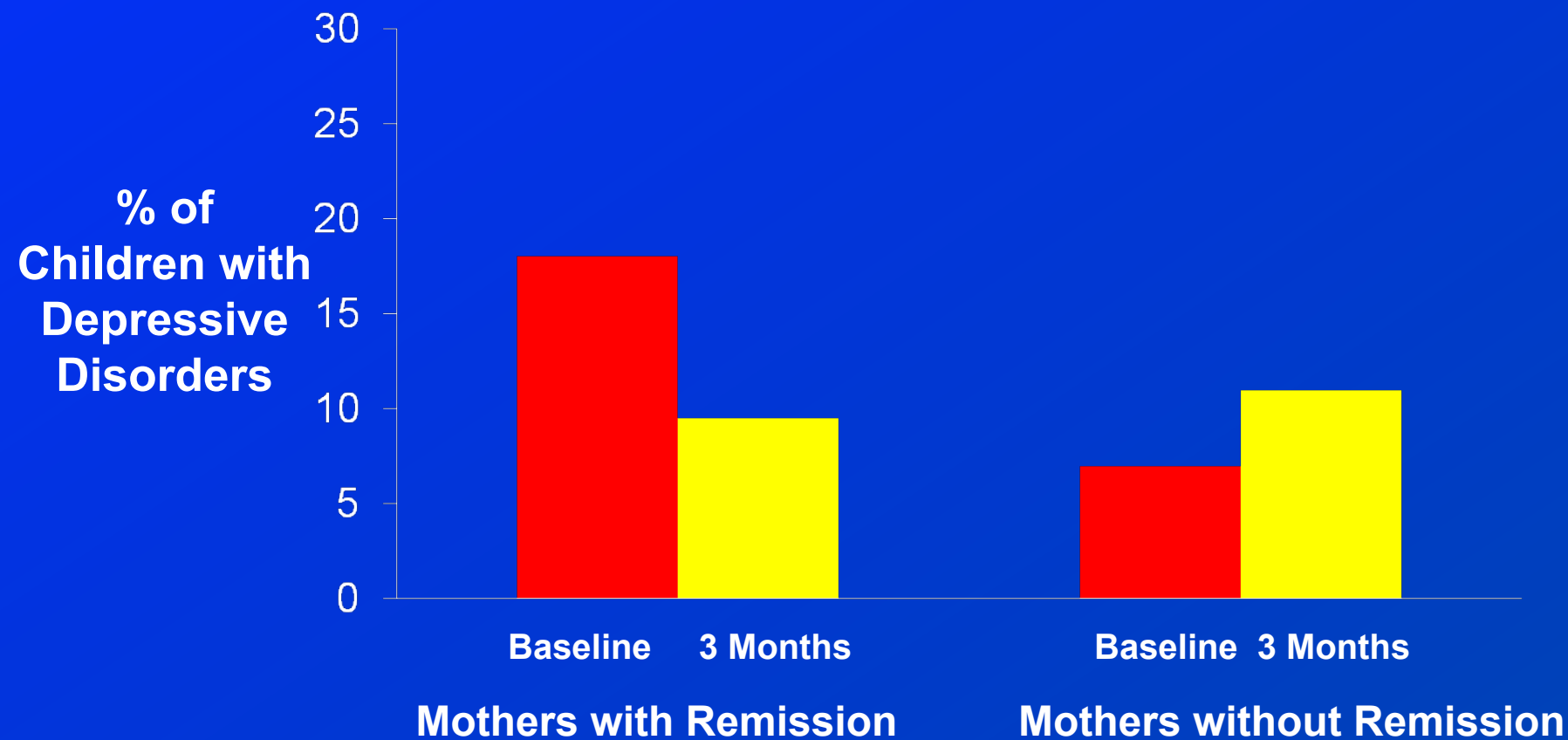
Meta-analysis of Antidepressant Trials Depression in Youth

	Response Rates
Antidepressants	61%

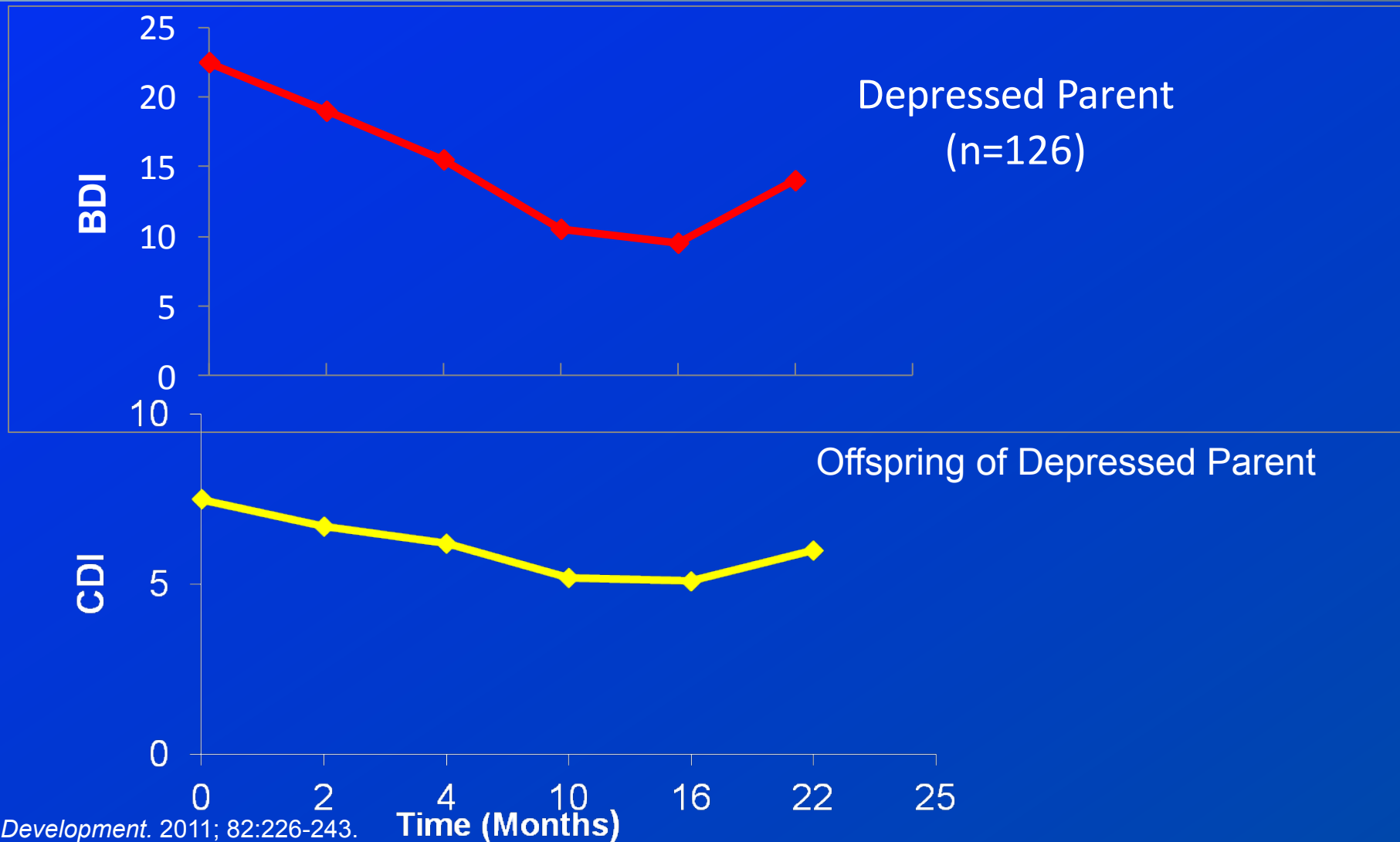
Predictors of Poorer Response to Acute Treatment Response

- More severe depression
- Baseline suicidality
- Comorbid disorders (anxiety, substance abuse)
- Hopelessness
- Family conflict

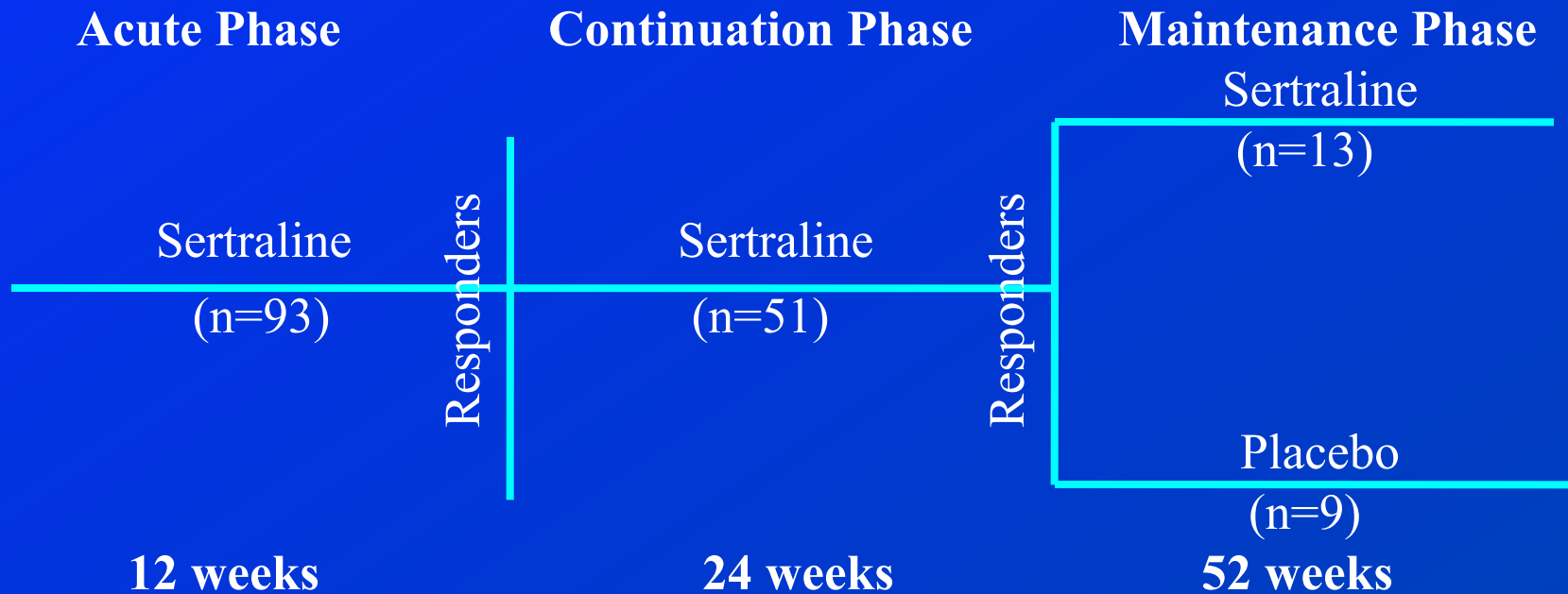
Remission in Maternal Depression and Children's Depression



Remission of Parental Depression



Maintenance Treatment for Adolescent Depression



Maintained response (no recurrence) at 52 weeks, %	
Sertraline	38
Placebo	0

Treatment of Adolescent Depression Study

- 439 adolescent outpatients with major depression
- Randomized to 12 weeks
 - Fluoxetine (10 mg/day to 40 mg/day)
 - CBT with fluoxetine (10 mg/day to 40 mg/day)
 - CBT alone
 - Placebo

CBT, cognitive behavioral therapy

Treatment for Adolescents with Depression Study (TADS) Study Team. *JAMA*. 2004;292:807-820.

Response Rates in Treatment for Adolescents with Depression Study (CGI ≤ 2)

Week	FLX + CBT	FLX	CBT	PLB
12	73%	62%	48%	35%
18	85%	69%	65%	
36	86%	81%	81%	

FLX, fluoxetine; PLB, placebo

Treatment for Adolescents with Depression Study (TADS) Study Team. *Arch Gen Psychiatry*. 2007;64:1132-1144; Kennard BD et al. *Am J Psychiatry*. 2009;166:337-344.

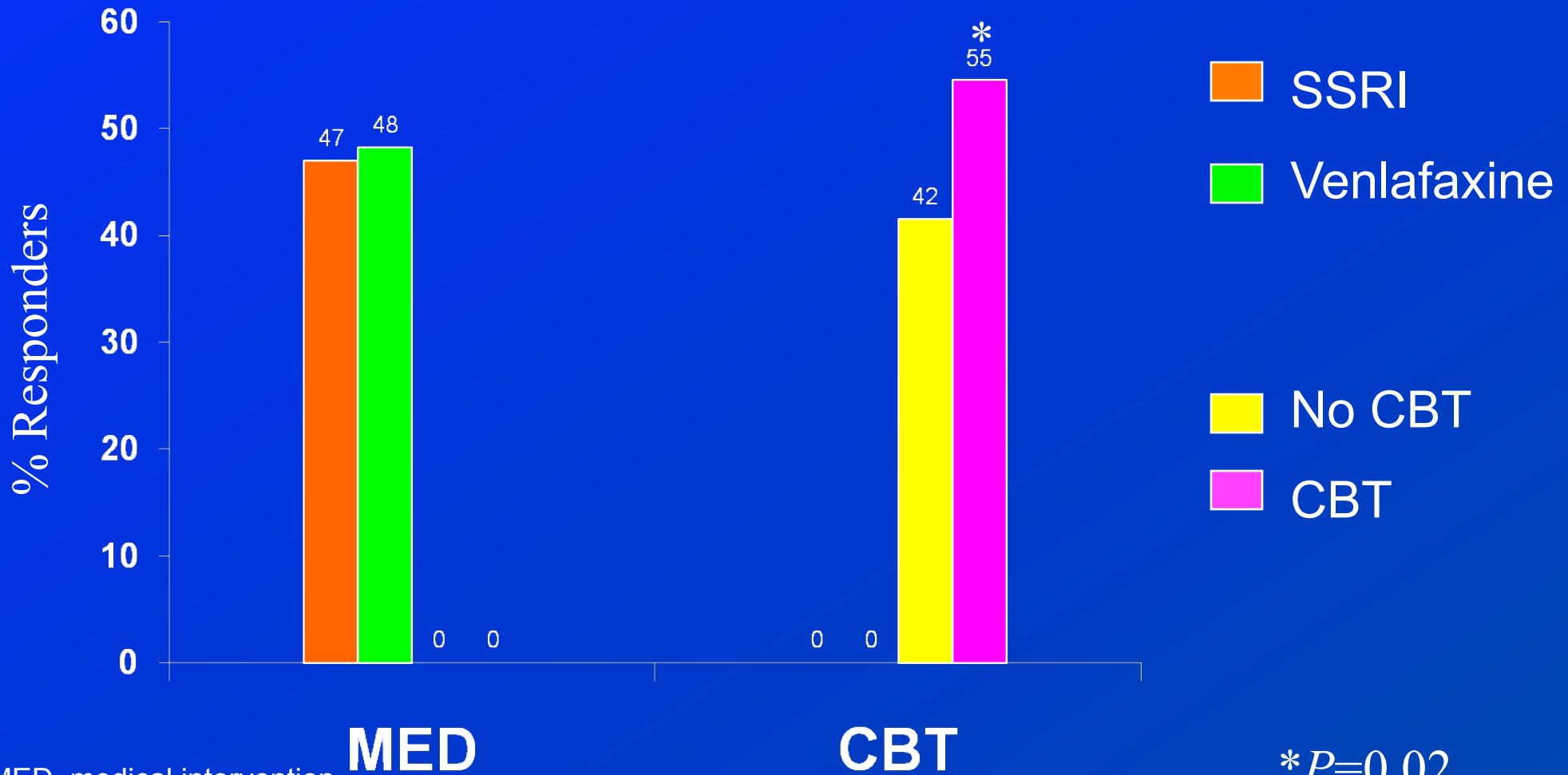
Treatment of SSRI-Resistant Depression in Adolescents Trial

- 334 adolescents with major depression who failed to respond to 8 weeks of SSRI
- Randomized to 12 weeks of:
 - Different SSRI
 - Different SSRI + CBT
 - Switch to venlafaxine
 - Switch to venlafaxine plus CBT

SSRI, selective serotonin reuptake inhibitor

Brent D et al. *JAMA*. 2008;299:901-913.

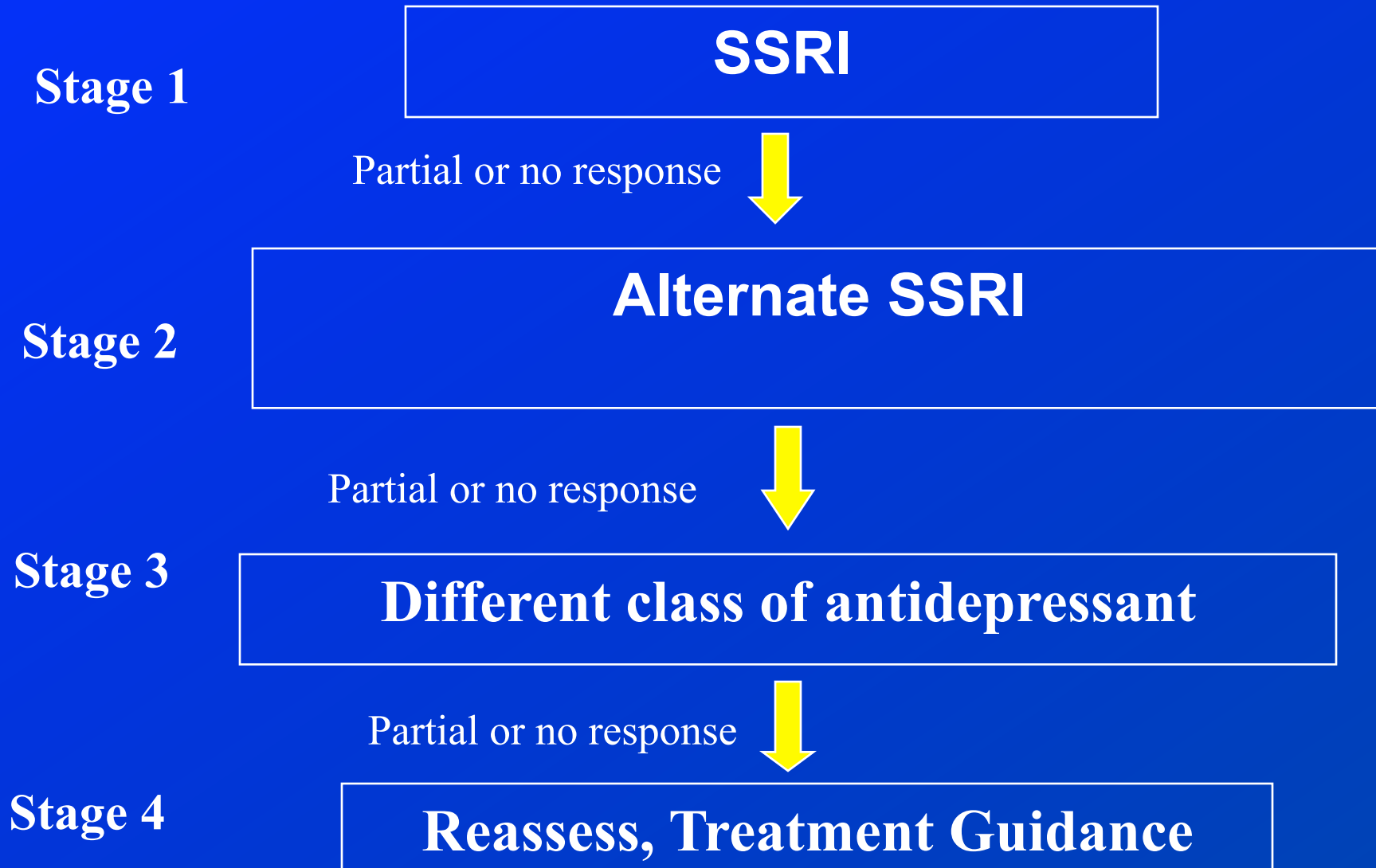
Clinical Response by Treatment Group (CGI ≤ 2 and decrease CDRS-R $\geq 50\%$)



MED, medical intervention

Brent D et al. *JAMA*. 2008;299:901-913.

Medication Algorithm for Depression in Children and Adolescents



Clinical Use of Antidepressants

Medication	Typical Starting Dose, mg/day		Target Dose, mg/day
	Child	Adolescent	
Citalopram	5-10	10	20-40
Escitalopram	5	10	10-20
Fluoxetine	5-10	10	20-40
Paroxetine	5-10	10	20-40
Sertraline	25	50	100-200
Mirtazapine	15	15	30-45
Venlafaxine	37.5	37.5	150-225
Bupropion	50 bid	50 bid	100-200
Duloxetine	20	20	60-120

Omega-3 Fatty Acids in Prepubertal Depression

- 28 children (ages 6 to 12 years) with first episode major depression randomized to Omega-3 (1000 mg/day; contained 400 mg EPA and 200 mg DHA) or placebo for 16 weeks

Groups	Response Rate, % (>50% Reduction in CDRS)	Remission, % (CDRS <29)
Omega-3	70	40
Placebo	0	0

DHA, docosahexaenoic acid

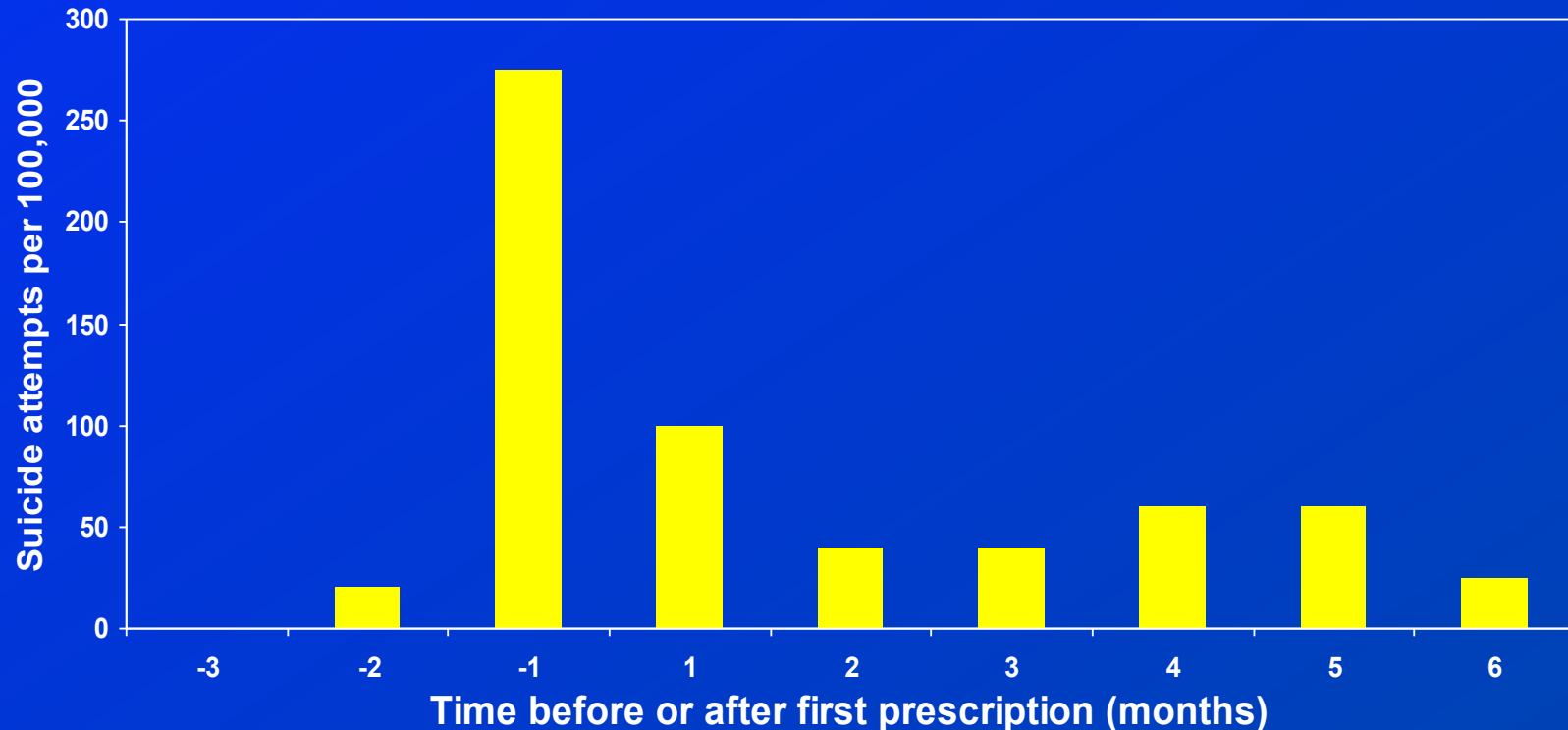
Nemets H et al. *Am J Psychiatry*. 2006;163(6):1098-1100.

Exercise for Adolescent Depression

- 13 adolescents with depression with low level of physical activity
- 12 week intervention
 - 15 supervised exercise sessions
 - 21 independent sessions
- Outcome
 - All participants completed protocol
 - Significant decrease in depression
(mean baseline CDRS-R 49; endpoint 29)

Suicide Risk During Antidepressant Treatment

- Computerized health plan records of patients less than 18 years old who received antidepressants (1992-2003)



(Simon et al, Am J Psychiatry 2006; 163:41-47)

Predictors of Suicidal Events in TADS

- Predictors of Suicidal Events
 - Higher levels of self-reported suicidal ideation and depression at baseline
 - Minimal improvement in depression
 - At least moderately depressed
 - Acute interpersonal conflict (73% of cases)

Summary

- Depression in children and adolescents is a serious illness
- The combination of antidepressant medication plus cognitive behavior therapy is more effective than each treatment alone