

# Depression in Childhood: Advances and Controversies in Treatment

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# Financial Disclosure (Past 12 months)

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# 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, 13-18 yrs
- Modified Version of World Health Organization Composite International Diagnostic Interview

	Sex		Age			Total	Severe Impairment
	Female %	Male %	13-14	15-16	17-18		%
<b>Major Depressive Disorder or Dysthymia</b>	15.9	7.7	8.4	12.6	15.4	11.7	8.7

# Incidence of Maternal and Paternal Depression

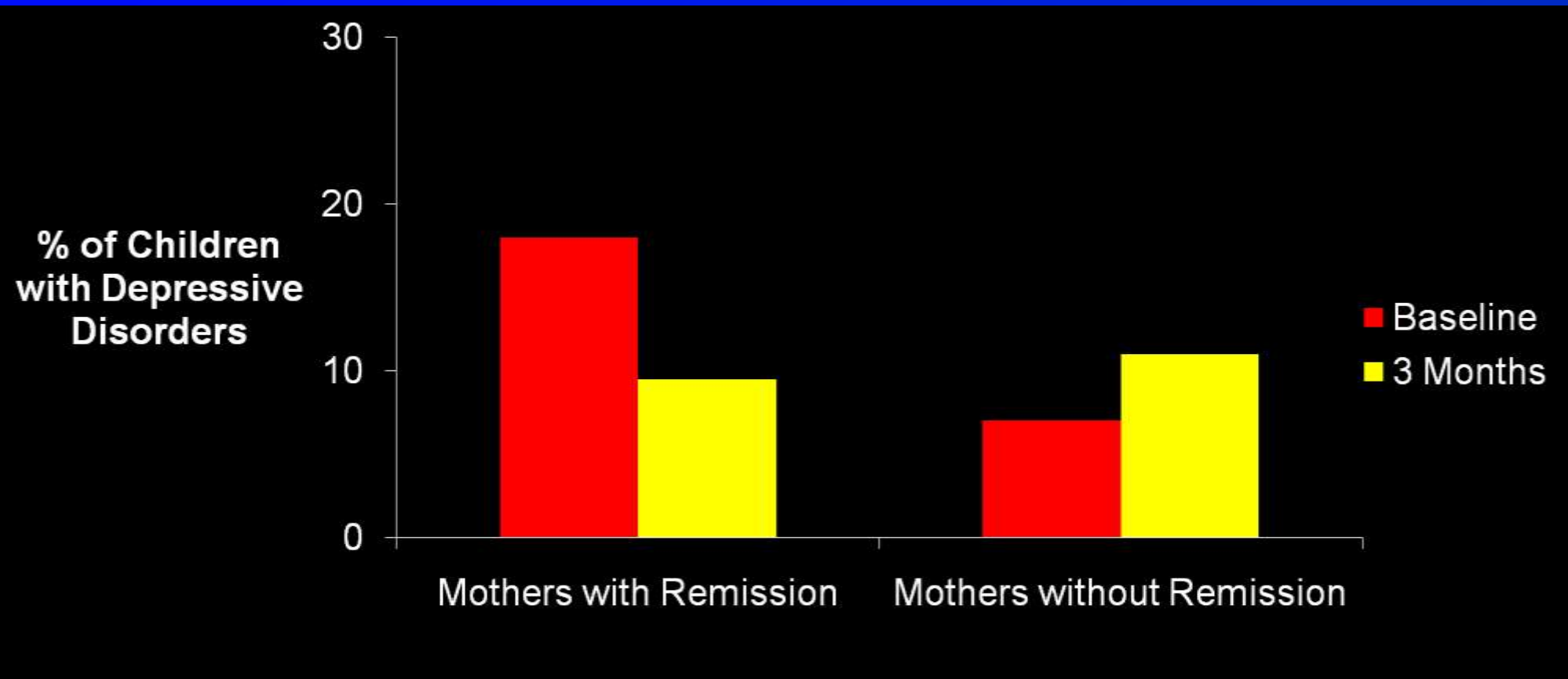
- Primary care records for 86,975 families

	Incidence of Depression (per 100 person years)
<b>Birth to 12 Years</b>	
<b>Mother</b>	<b>7.5</b>
<b>Father</b>	<b>2.3</b>
<b>First Year Postpartum</b>	
<b>Mother</b>	<b>13.9</b>
<b>Father</b>	<b>3.6</b>

Risk Factors: Parental history of depression, younger parents, low SES

Davé S et al. Arch Pediatr Adolesc Med, 2010 Sept 6 (Epub ahead of print)

# Remission in Maternal Depression and Children's Depression



# Course of Childhood Depression

- Recovery from initial episode
  - 85% – 92%
  - Mean time to recovery: 9 – 17 months
- Recurrence after recovery
  - 40% – 42%
  - Mean time to recurrence: 3 – 4 years

# Neuroendocrine and Psychological Predictors Course of Adolescent Depression

- 55 adolescents with major depression
- Urinary free cortisol measures during index episode
- Assessment of environmental stress and social support
- **Five year follow-up**
  - Higher cortisol levels, longer time to recovery
  - Effect of cortisol on recovery moderated by social support
  - Elevated cortisol plus recent stressful experiences predicted recurrence
  - Higher social support protective against recurrence



# Adulthood Outcomes of Child and Adolescent Depression

- 113 adolescents with major depression
- Follow-up 8 years
  - 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>
<b>Fluoxetine</b>	<b>8-17</b>
<b>Escitalopram</b>	<b>12-17</b>

# FDA Approval for Maintenance Treatment of Major Depressive Disorder

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

# Controlled Pediatric Depression Trials

	Medication	Ages	Number of Studies
<b>Positive* Studies</b>	Citalopram	7-17	1
	Sertraline	6-17	2 (a priori pooled analysis)**
<b>Negative* Studies</b>	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](http://www.fda.gov/cder/foi/esum/2004/20152s032_serzone))

# Antidepressant Response Rates in Child and Adolescent Studies

Response Rates  
(CGI-I  $\leq 2$ )

## Positive Studies

### Medication

### Placebo

Fluoxetine

52%

37%

56%

33%

61%

35%

Citalopram

47%

45%

Escitalpram

64%

53%

Sertraline

63%

53%

# Antidepressant Response Rates in Child and Adolescent Studies

Response Rates (CGI-I  $\leq 2$ )

## Negative Studies

### Medication

### Placebo

Paroxetine

69%

57%

66%

48%

49%

46%

Escitalopram

63%

52%

Mirtazapine

60%

57%

54%

41%

Nefazodone

63%

44%

65%

46%

Venlafaxine

68%

61%

50%

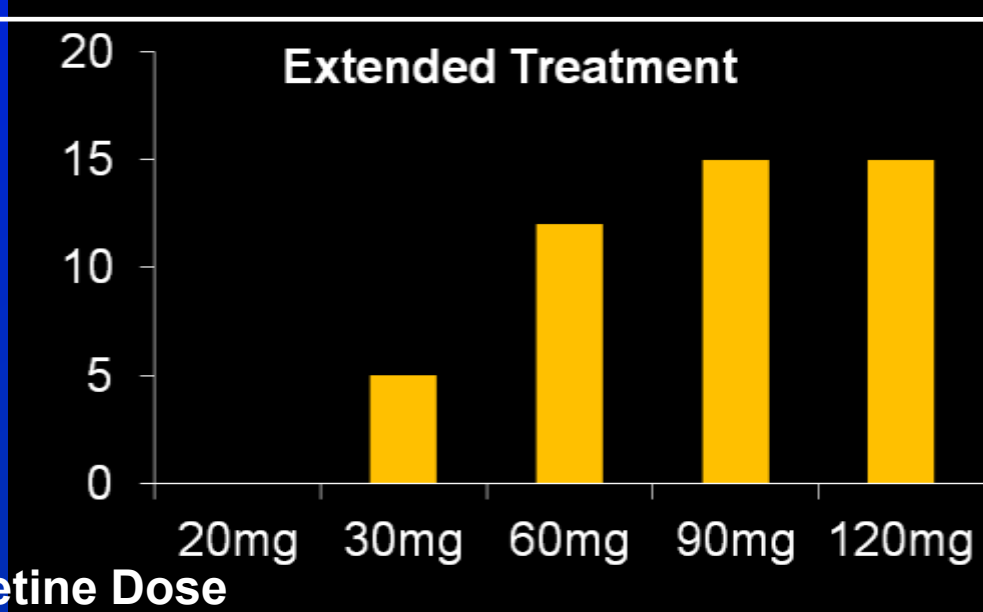
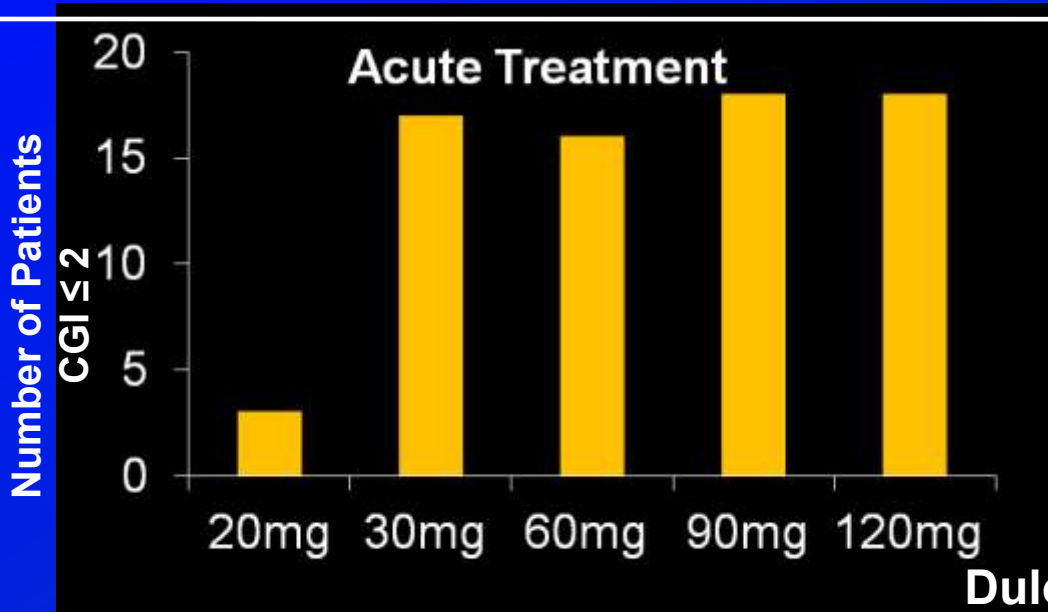
41%

# Placebo Response in Pediatric Depression Trials

- Predictors of response (CGI  $\leq$  2) to placebo in 12 randomized controlled antidepressant trials for pediatric major depression disorder
- Predictors of Placebo Response
  1. Number of study sites
  2. Baseline severity of illness (lower)
  3. Younger age

# Open-Label Study of Duloxetine for Major Depression in Children and Adolescents

- 72 children and adolescents, ages 7 to 17 years, with major depression
- Open label duloxetine (20-120mg/day) over 30 weeks



**55 (76%) required duloxetine doses of 60, 90 and 120mg once daily for efficacy**



# Omega-3 Fatty Acids in Prepubertal Depression

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

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

# Treatment of Adolescent Depression Study (TADS)

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

# Response Rates in TADS (CGI $\leq$ 2)

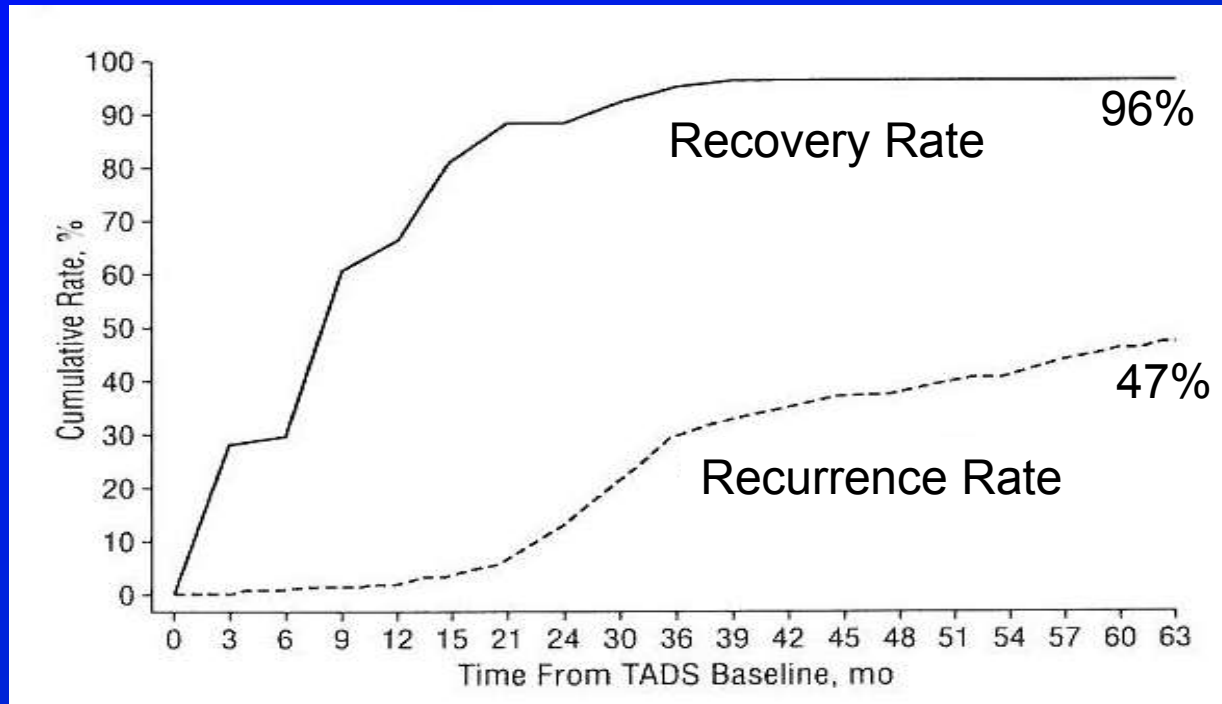
Week	FLX + CBT	FLX	CBT	PLB	PLB/Open
12	73%	62%	48%	35%	
18	85%	69%	65%		67%
36	86%	81%	81%		82%

# Remission Rates in TADS

Remission Rate (CDRS-R $\leq$ 28)					
Week	FLX+CBT	FLX	CBT	PBO	PBO/Open
<b>12</b>	39%	24%	19%	19%	
<b>18</b>	56%	37%	27%		34%
<b>36</b>	<b>60%</b>	<b>55%</b>	<b>64%</b>		48%

- Greater the number of residual depressive symptoms at week 12, less likelihood of subsequent remission

# TADS: Five Year Follow-Up



- Higher recurrence among females (57%) than males (33%)

*Recovery: no clinically significant MDD symptoms for  $\geq 8$  weeks*

*Recurrence: new episode of MDD following recovery*

# Predictors of Treatment Response in TADS

- Younger adolescents
- Less chronically depressed
- Higher functioning
- Less hopeless with less suicidal ideation
- Fewer melancholic features
- Fewer comorbid disorders
- Greater expectations for improvement

(Curry et al, J Am Acad Child Adolesc Psychiatry 2006;45:1427-1439)

# Predictors of Suicidal Events in TADS

- Suicidal Events
  - 44 (10%) had suicidal events (attempts, ideation)
  - Events occurred .4 - 31 weeks (mean 12 weeks) after treatment;
    - No timing differences between medication versus nonmedication groups

# Predictors of Suicidal Events in TADS

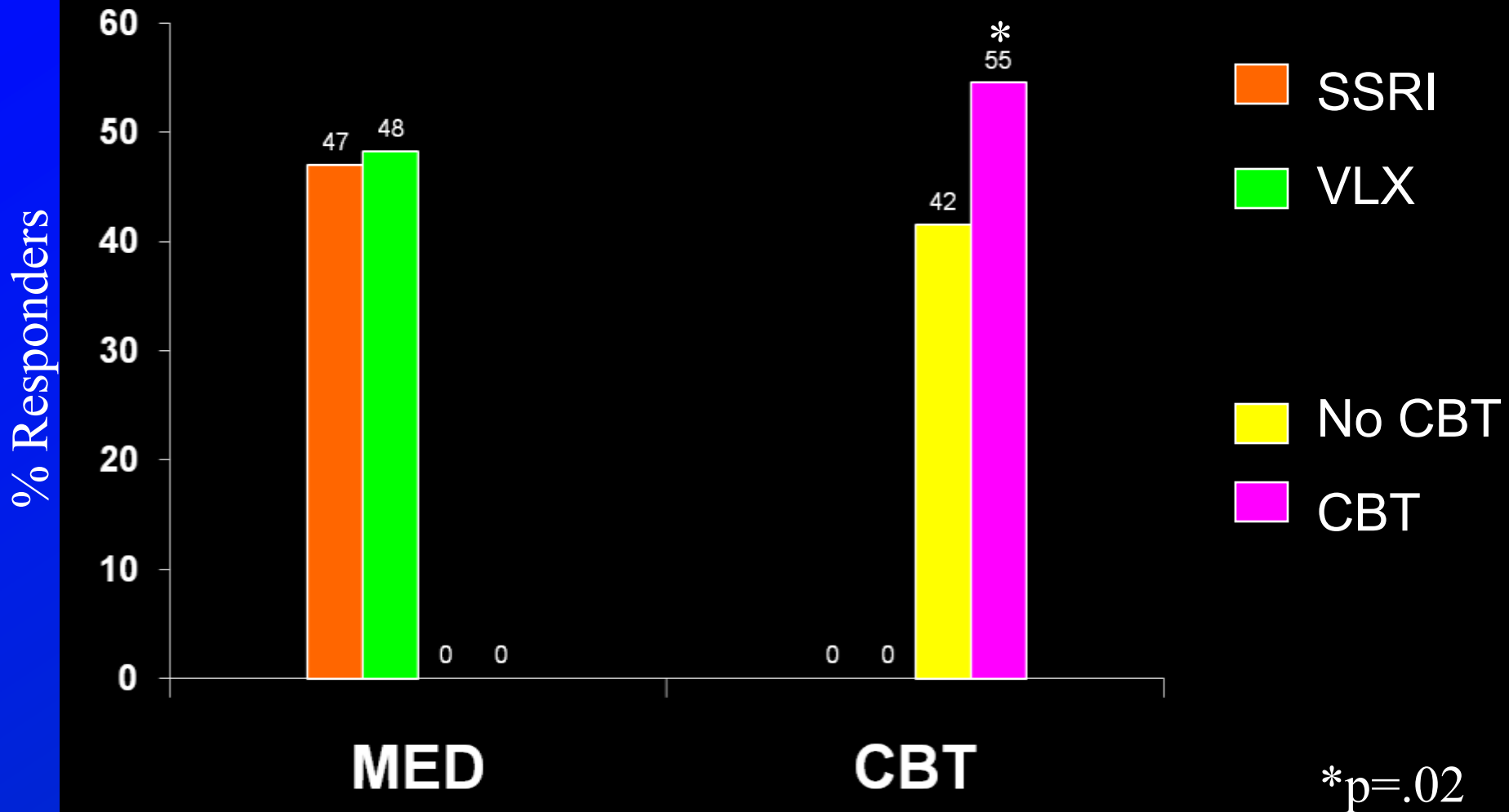
- Predictors of Suicidal Events
  - Higher levels of self-reported suicidal ideation and depression at baseline
  - Minimal improvement in depression
  - At least moderately depressed
  - Acute interpersonal conflict (73% of cases)
- No Association with Suicidal Events
  - Irritability
  - Mania
  - Sleep problems
  - History of substance abuse
  - Akathisia
  - Comorbidity
  - Hopelessness



# Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) 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

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



# Predictors of Treatment Response in TORDIA

- Predictors of better response
  - Less severe depression
  - Less family conflict
  - Absence of nonsuicidal self-injurious behavior
- Combined treatment (CBT+ Medication) superior to medication
  - More comorbid disorders
  - No abuse history
  - Lower hopelessness

# Adverse Events

	<b>SSRI</b> N=168 %	<b>Venlafaxine</b> N=166 %	<b>No CBT</b> N=168 %	<b>CBT</b> N=166 %
≥1 Serious Adverse Event	11	11	8	14
Harm-related <sup>a</sup>	19	22	19	22
≥ 1 Adverse Event	51	47	50	48
Suicide attempts	4	7	4	6
Skin <sup>b</sup>	2	8	4	5

<sup>a</sup>Defined as suicidal ideation, suicide attempt, or self-injurious behavior;

<sup>b</sup>By medication:  $\chi^2=6.69$ ,  $p=.01$ ;

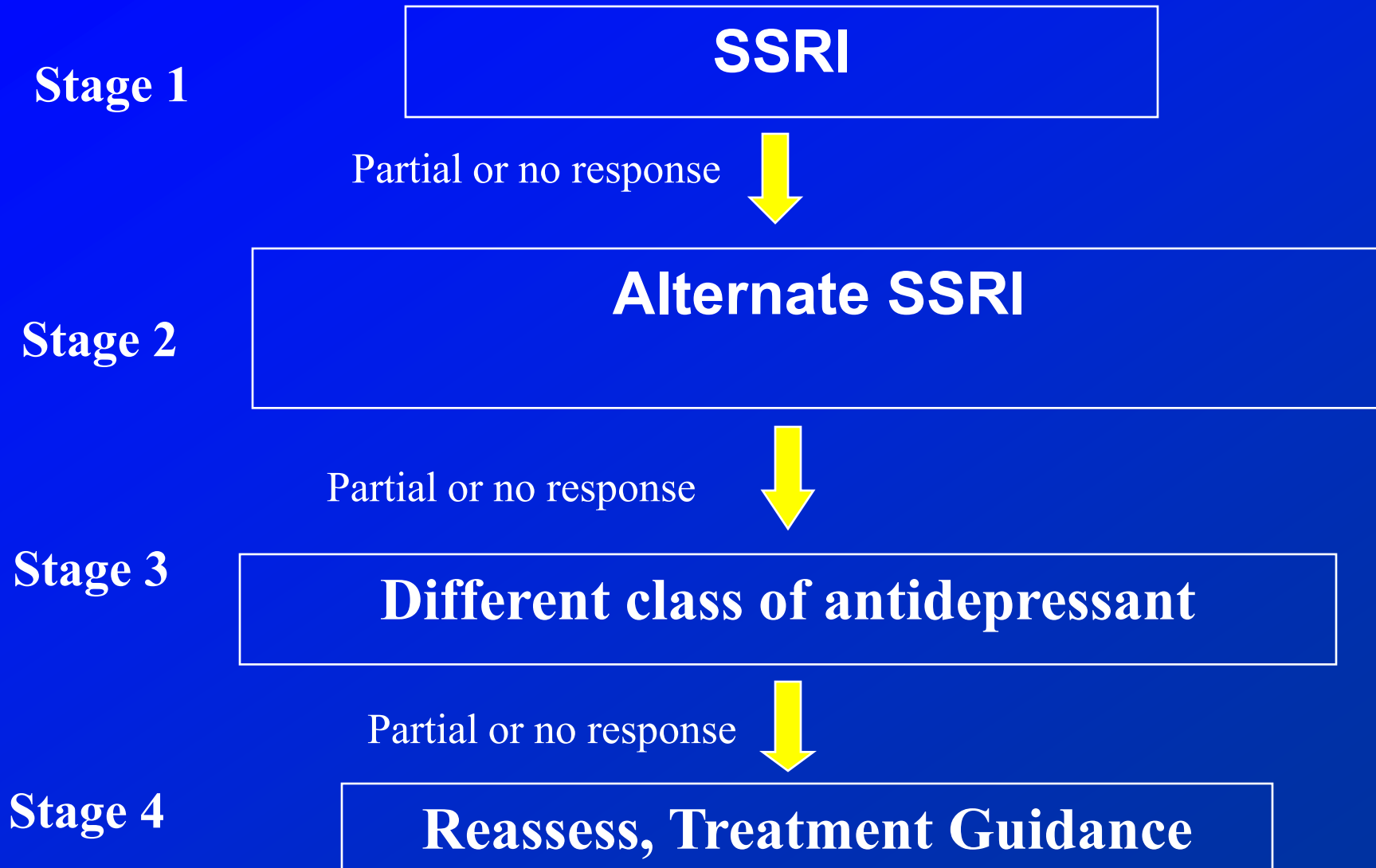
# Predictors of Suicidal Adverse Events in TORDIA

- During first 12 weeks of treatment
  - Suicidal self injury was 14%
- Median time to suicidal event was 3 weeks
- Predictors of suicidal event
  - High baseline suicidal ideation
  - Family conflict
  - Drug or alcohol use

# TORDIA: 24 Week Outcomes

- 39% achieved remission
- Initial treatment assignment did not affect remission rates
- Remission higher with lower baseline depression, hopelessness, and self-reported anxiety
- Clinical response by week 12
  - Increases likelihood of remission (62% vs 18%)
  - Faster time to remission (12 wks vs 18 wks)

# Treatment Algorithm for Childhood Depression

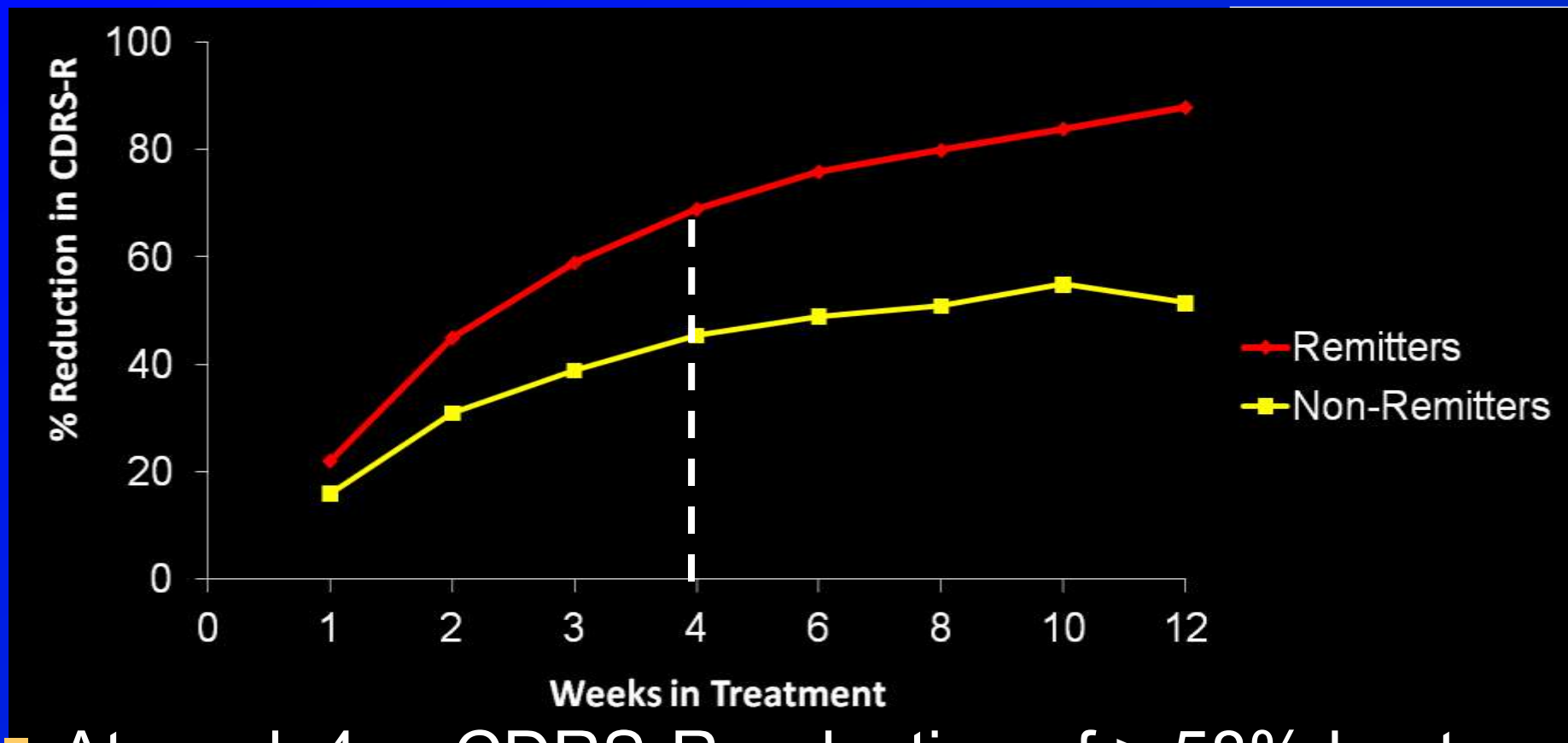


# Clinical Use of Antidepressants

Medication	Typical Starting Dose		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



# Acute Antidepressant Response and Remission in Pediatric Depression

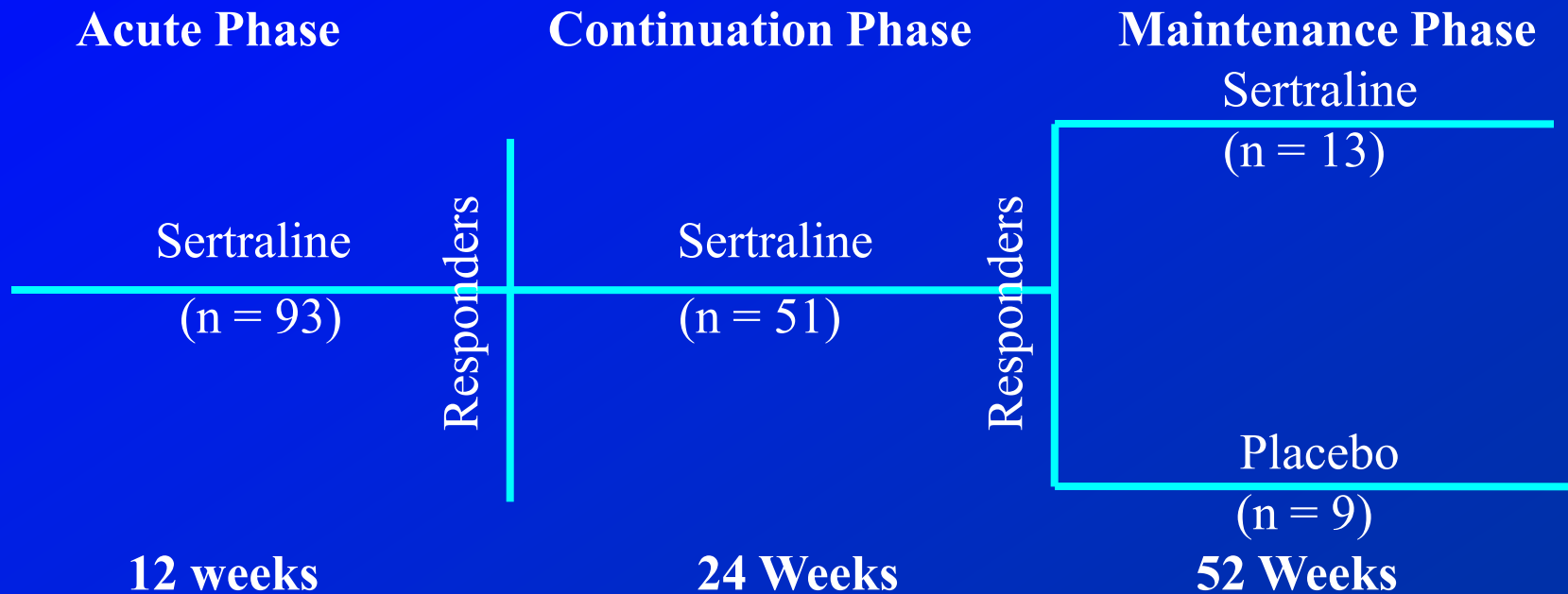


oxetine

- At week 4, a CDRS-R reduction of  $> 58\%$  best discriminates remitters from non-remitters

(Tao et al, J Am Acad Child Adolesc Psychiatry, 2009; 48:71-78)

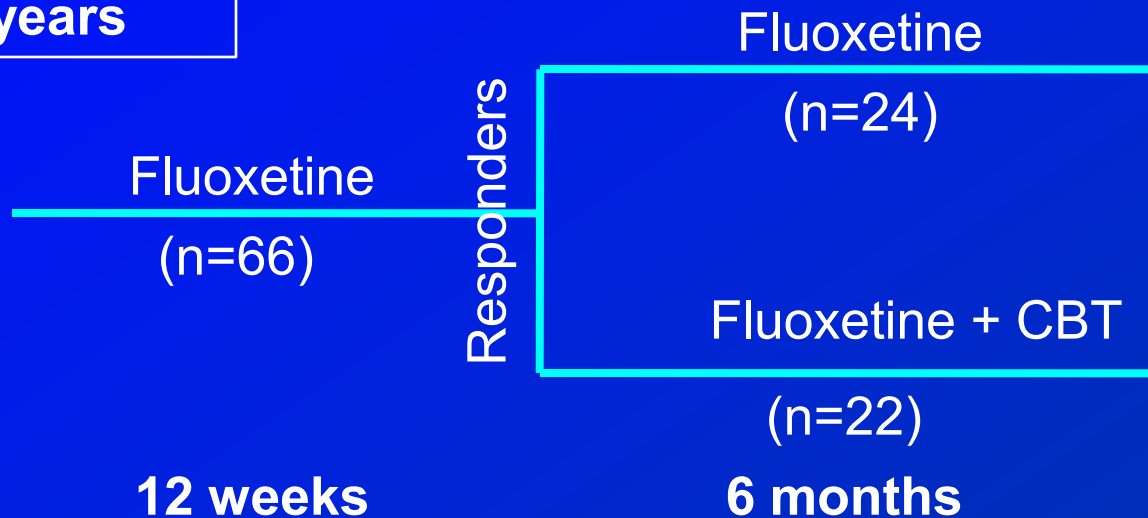
# Maintenance Treatment for Adolescent Depression



Maintained Response (No Recurrence) at 52 Weeks	
38%	Sertraline
0%	Placebo

# CBT to Prevent Relapse in Pediatric Depression

Ages 11-18 years



## Relapse Rates at 6 Months

(CDRS-R $\geq$ 40 and 2 weeks symptom worsening or clinical deterioration)

37%

Fluoxetine

15%

Fluoxetine + CBT

# Box Warning on Antidepressants

- Increase risk of suicidal thinking and behavior (suicidality) in children and adolescents treated with antidepressants
- Applies to all antidepressants

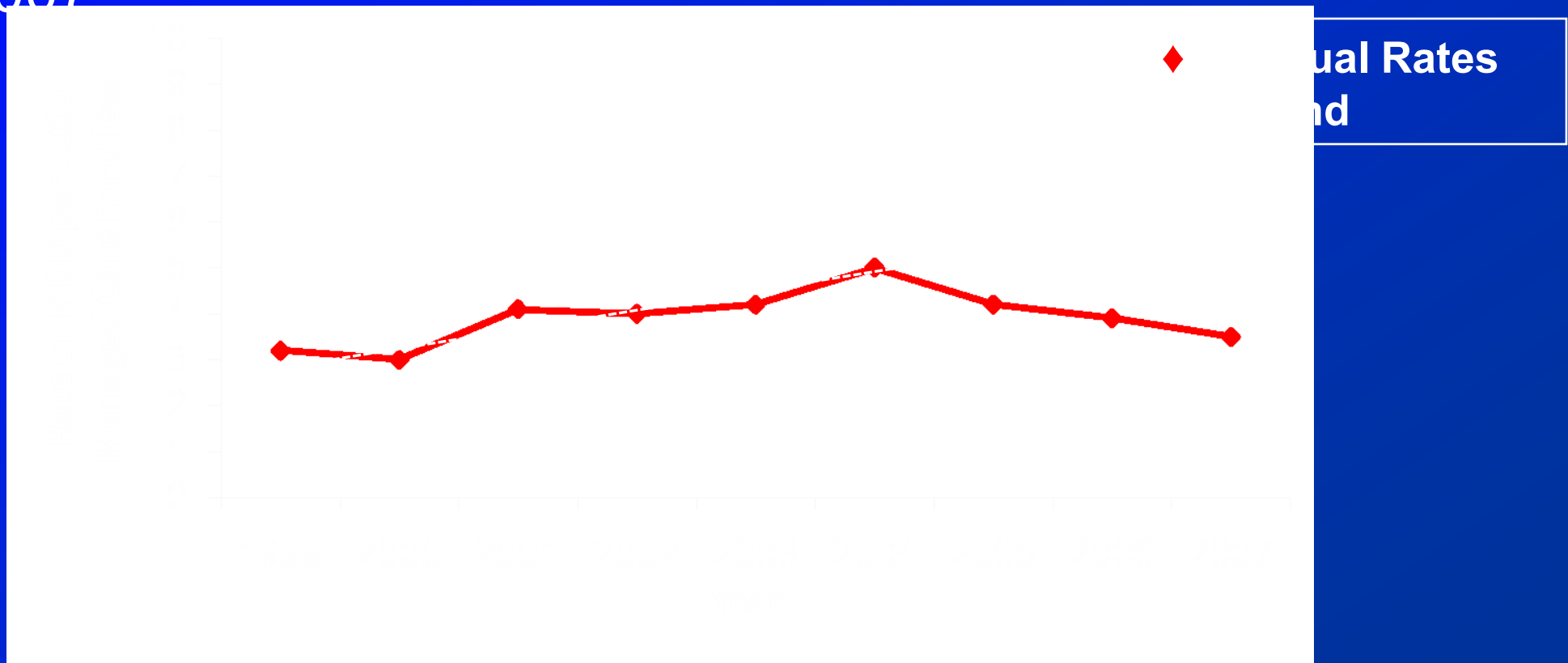
## Revision

- Depression associated with increase in risk of suicide
- Monitor appropriately and observe closely for clinical worsening, suicidality or unusual changes in behavior

(FDA News, 2004; FDA News 2007)

# Depression Diagnosis After FDA Warnings

- 91,748 patients (ages 5-18) with new episodes of depression
- National managed care claims database June 1999-June 2007



# Depression Treatment After FDA Warnings

- 44% decrease in primary care provider diagnoses of depression
- Increase in diagnoses by non-psychiatrist mental health providers
- No significant increase in psychotherapy
- Significant decrease (10%) in selective serotonin inhibitor use; 40% decrease for primary care providers

# Comparative Safety of Antidepressants

- 9 year cohort study of British Columbia youth, 10-18 yrs old
- 20,906 youth with depression began antidepressant treatment 1997-2005

	Rate Ratio
	<u>Suicidal Acts</u>
<b>SSRIs</b>	
<b>Citalopram</b>	.97
<b>Fluvoxamine</b>	1.05
<b>Paroxetine</b>	.80
<b>Sertraline</b>	1.02
<b>SNRIs</b>	1.36
<b>Tricyclics</b>	.92

# Efficacy vs. Suicidal Risk of Antidepressants in Pediatric Patients

- Meta-analysis of 27 trials of pediatric major depression

<b>Number Needed to Treat</b>	<b>10</b>
<b>Number Needed to Harm</b>	<b>112</b>

	<u>Suicidal Ideation/attempts</u>
Antidepressants	3%
Placebo	2%

(Bridge et al, JAMA 2007;297:1683-1696)



# Summary

- High placebo response rate in pediatric depression trials
- Alternative treatment designs (e.g. comparator trials) to demonstrate efficacy
- Studies designed to assess suicidality and antidepressants are warranted
- Maintenance studies are needed to assess long term efficacy and safety of antidepressants