Depression in Childhood: Advances and Controversies in Treatment

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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		%
Major Depressive Disorder or Dysthymia	15.9	7.7	8.4	12.6	15.4	11.7	8.7

Merikangas KR et al, JAACAP 2010; 49:980-989

Incidence of Maternal and Paternal Depression

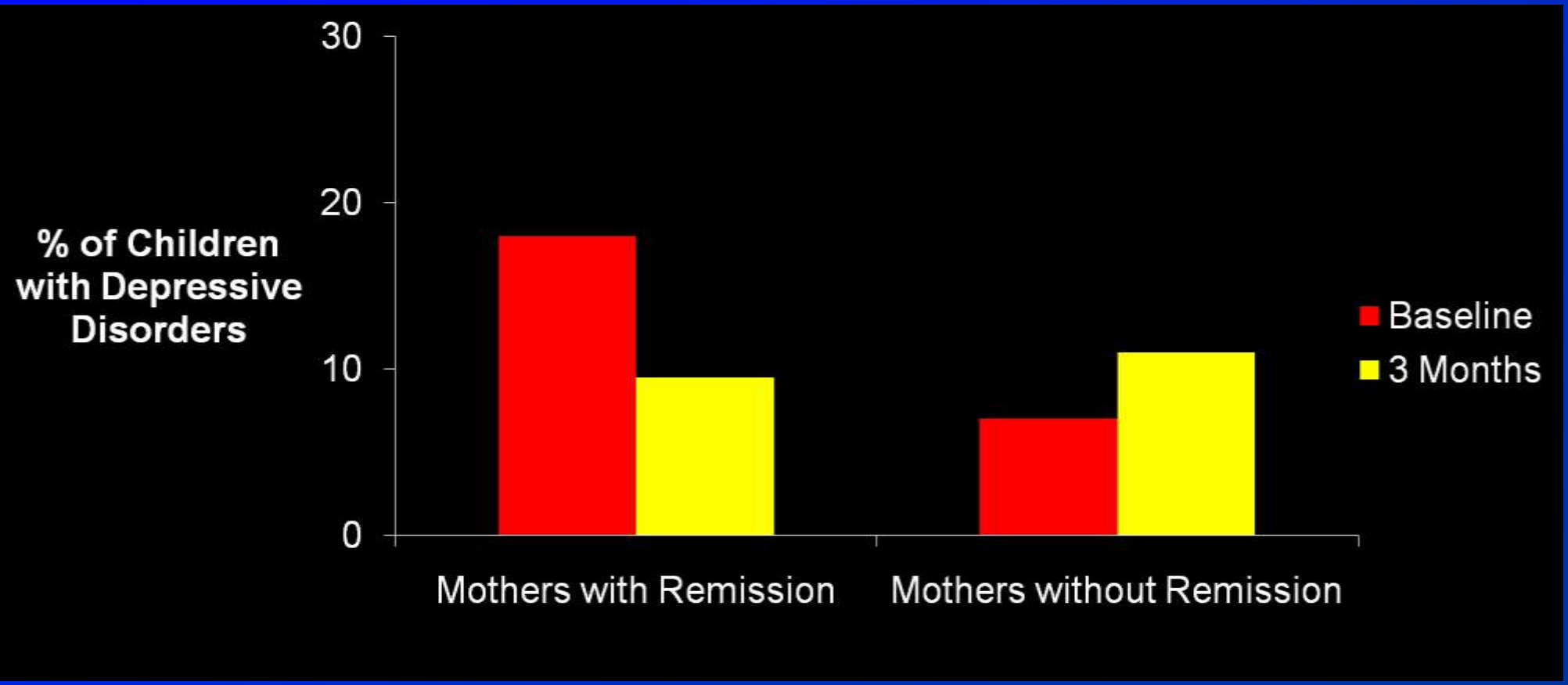
- Primary care records for 86,975 families

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

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



Weissman MM et al. JAMA 2006; 295:1389-1398

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

Rao U et al. J Am Acad Child Adolesc Psychiatry 2010; 49:141-151;
Birmaher et al, J Am Acad Child Adolesc Psychiatry 2004;43:63-70

Neuroendrocrine 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

Rao U et al, J am Acad Child Adolesc Psychiatry 2010; 49:141-151

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

Dunn & Goodyer, Br J Psychiatry 2006;188:216-222

FDA Approval for Acute Treatment of Major Depressive Disorder

Medication	Ages
Fluoxetine	8-17
Escitalopram	12-17

FDA Approval for Maintenance Treatment of Major Depressive Disorder

Medication	Ages
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)

Antidepressant Response Rates in Child and Adolescent Studies

	Response Rates (CGI-I ≤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 ≤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

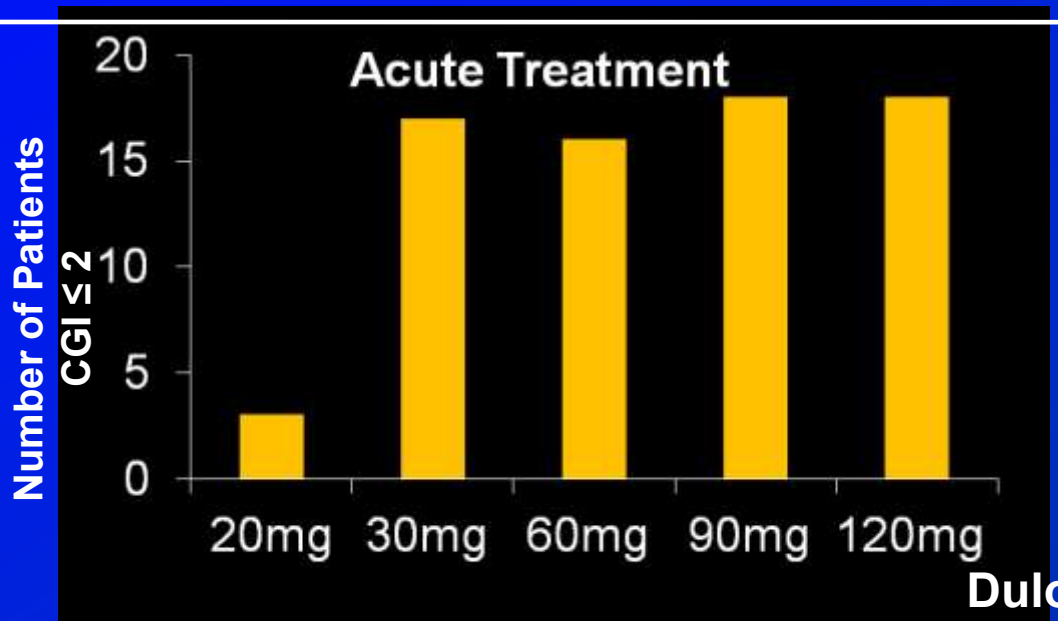
- Predictors of response (CGI ≤ 2) to placebo in 12 randomized controlled antidepressant trials for pediatric major depression disorder

- Predictors of Placebo Response
  1. Number of study sites
  2. Baseline severity of illness (lower)
  3. Younger age

(Bridge et al, Am J Psychiatry 2009; 166(1):42-49

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

March et al, 49th Annual NCDEU Meeting, Hollywood, FL; June 29th-July 2nd 2009

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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%

Nemets et al, Am J Psychiatry 2006; 163:1098-1100

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

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

Response Rates in TADS (CGI ≤ 2)

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

(TADS Team, Arch Gen Psychiatry 2007;64:1132-1144; Kennard et al Am J Psychiatry 2009; 166:337-344)

Remission Rates in TADS

Remission Rate (CDRS-R≤28)					
Week	**FLX+CBT**	**FLX**	**CBT**	**PBO**	**PBO/Open**
12	39%	24%	19%	19%	
18	56%	37%	27%		34%
36	**60%**	**55%**	**64%**		48%

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

(Kennard et al, J. Am Acad. Child Adolesc. Psychiatry 2009; 48:186-195)

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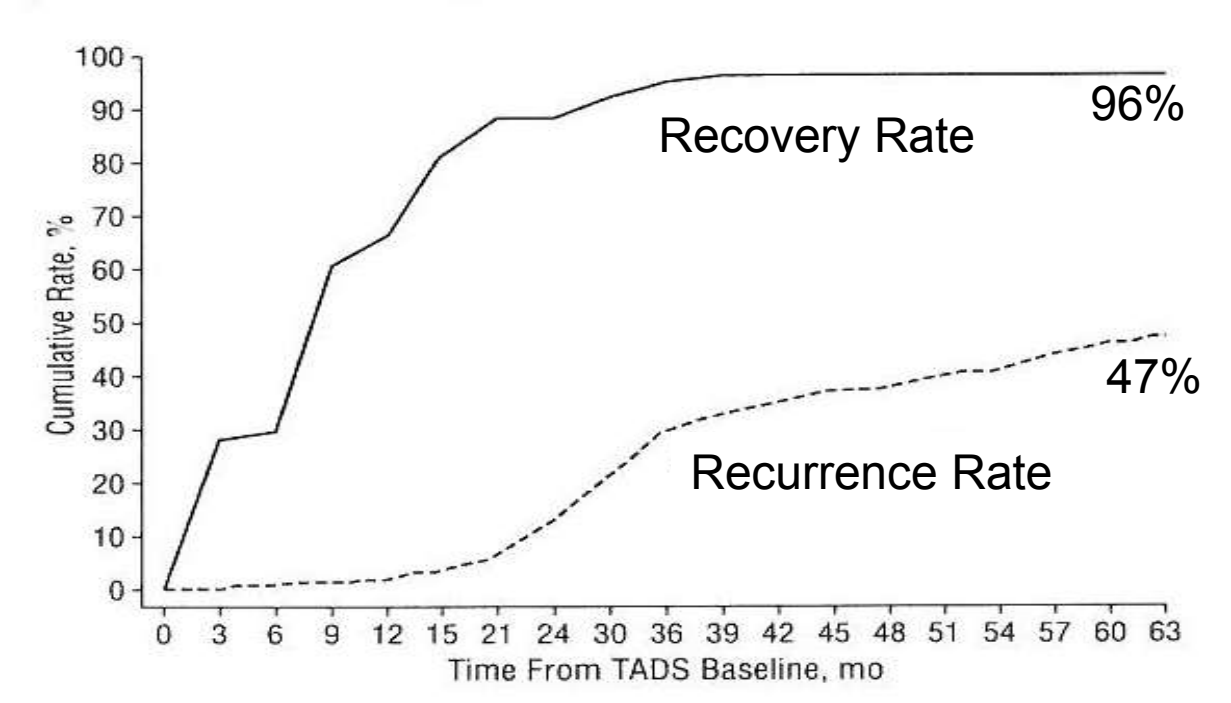
TADS: Five Year Follow-Up



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

Recovery: no clinically significant MDD symptoms for ≥ 8 weeks
Recurrence: new episode of MDD following recovery

Curry J et al, Arch Gen Psychiatry. Published online November 1 2010. doi:10.1001/archgenpsychiatry.2010.150

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

(Vitiello et al, J Clin Psychiatry 2009; 70:741-747)

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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

(Vitiello et al, J Clin Psychiatry 2009; 70:741-747)

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

(Brent et al, JAMA 2008;299:901-913)

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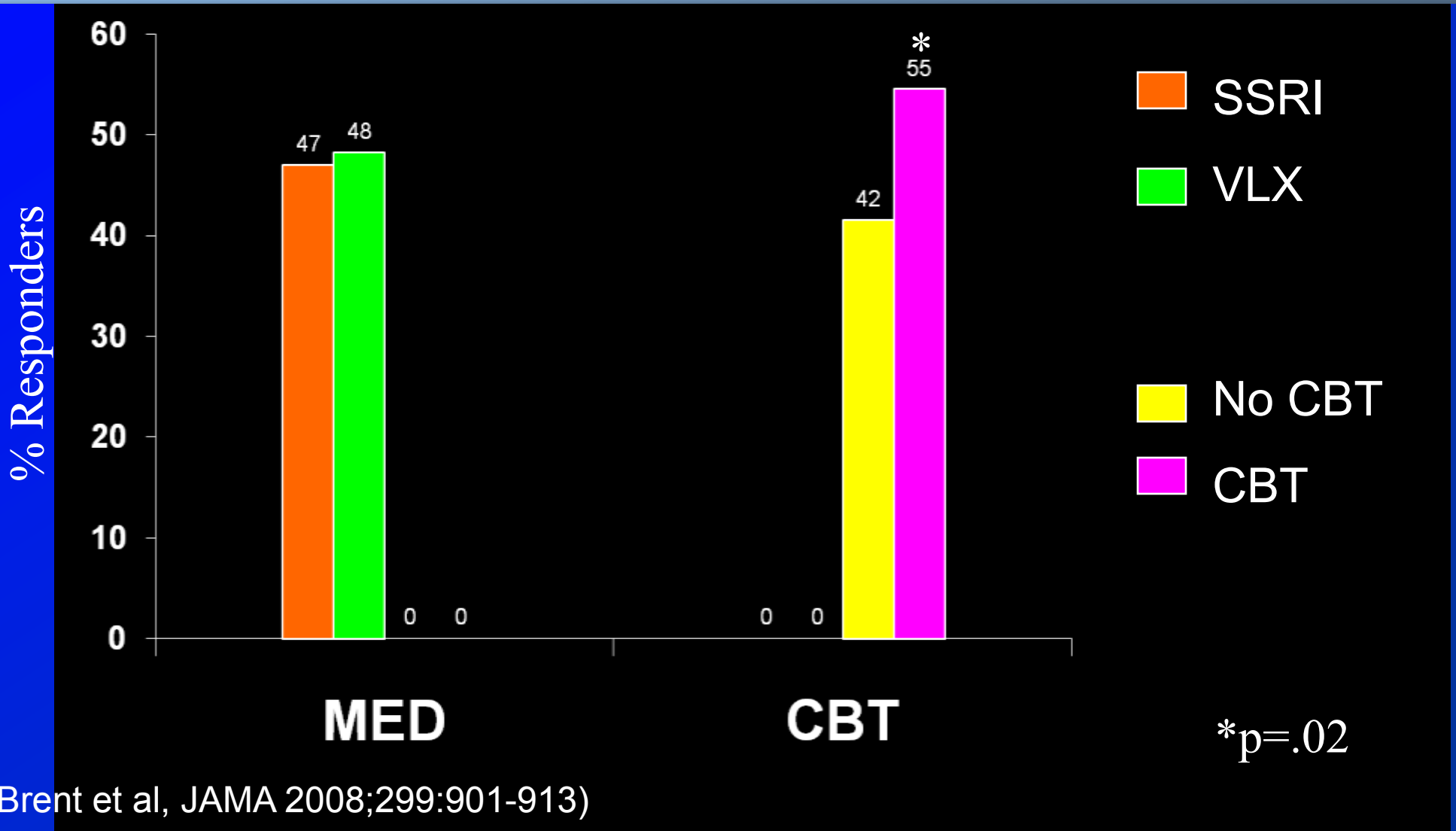
Clinical Response by Treatment Group (CGI≤2 and decrease CDRS-R≥50%)



(Brent et al, JAMA 2008;299:901-913)

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

Asarnow et al. J Am Acad Child Adolesc Psychiatry 2009; 48:330-339

Adverse Events

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

[a]Defined as suicidal ideation, suicide attempt, or self-injurious behavior;
[b]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

Brent et al, Am J Psychiatry 2009; 166:418-426

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)

Emslie GJ et al, Am J Psychiatry 2010; 167:782-791

Treatment Algorithm for Childhood Depression

Stage 1

SSRI

Partial or no response

Stage 2

Alternate SSRI

Partial or no response

Stage 3

Different class of antidepressant

Partial or no response

Stage 4

Reassess, Treatment Guidance

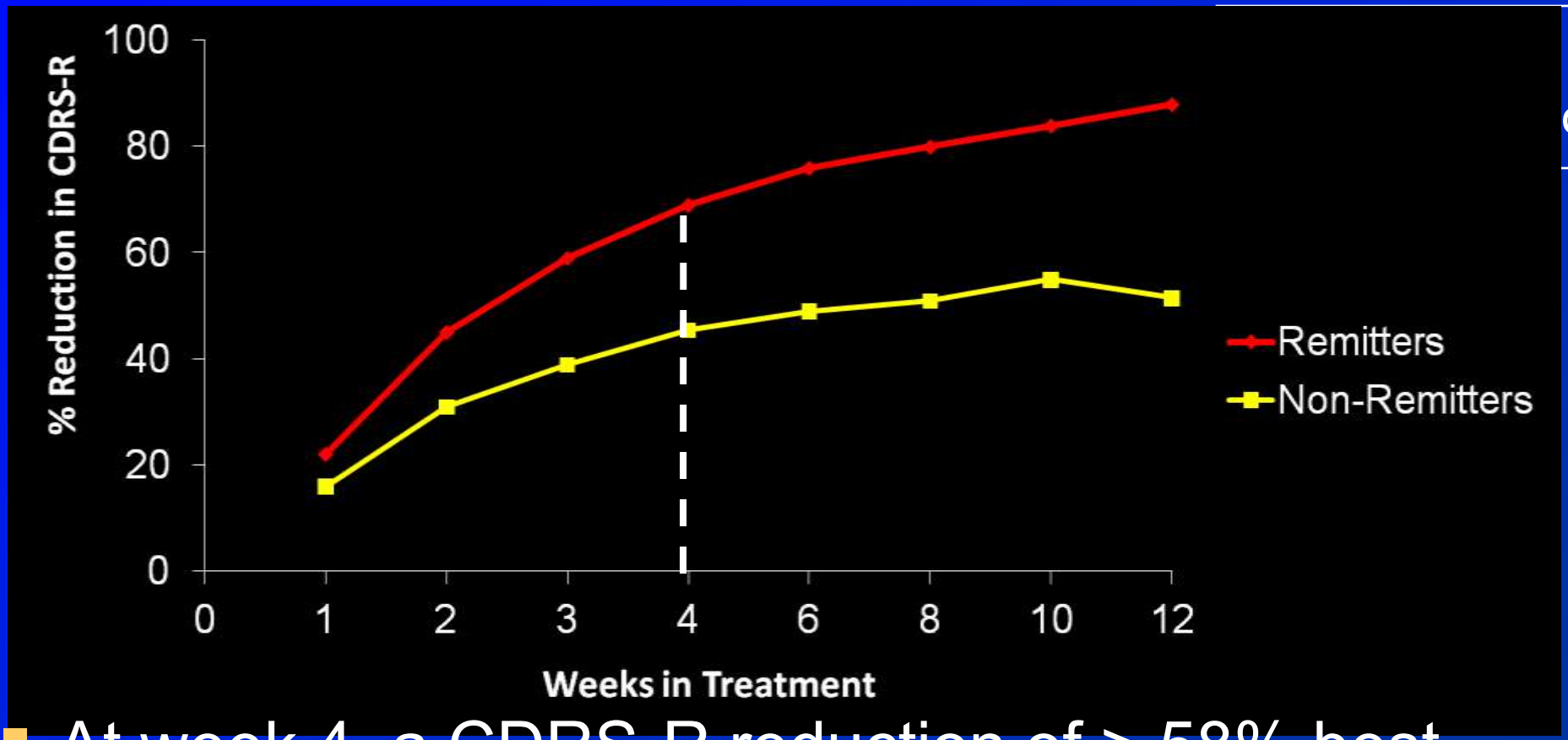
(Hughes et al, JAACAP 2007;46(6)667-686)

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

Adapted from: Wagner, K.D., Pliska, S.R (2009). Treatment of Child and Adolescent Disorders. In Schatzberg, A.F., & Nemeroff, C.B. (Eds.), The American Psychiatric Publishing Textbook of Psychopharmacology (1309-1372). Washington, DC: American Psychiatric Publishing, Inc.

Acute Antidepressant Response and Remission in Pediatric Depression

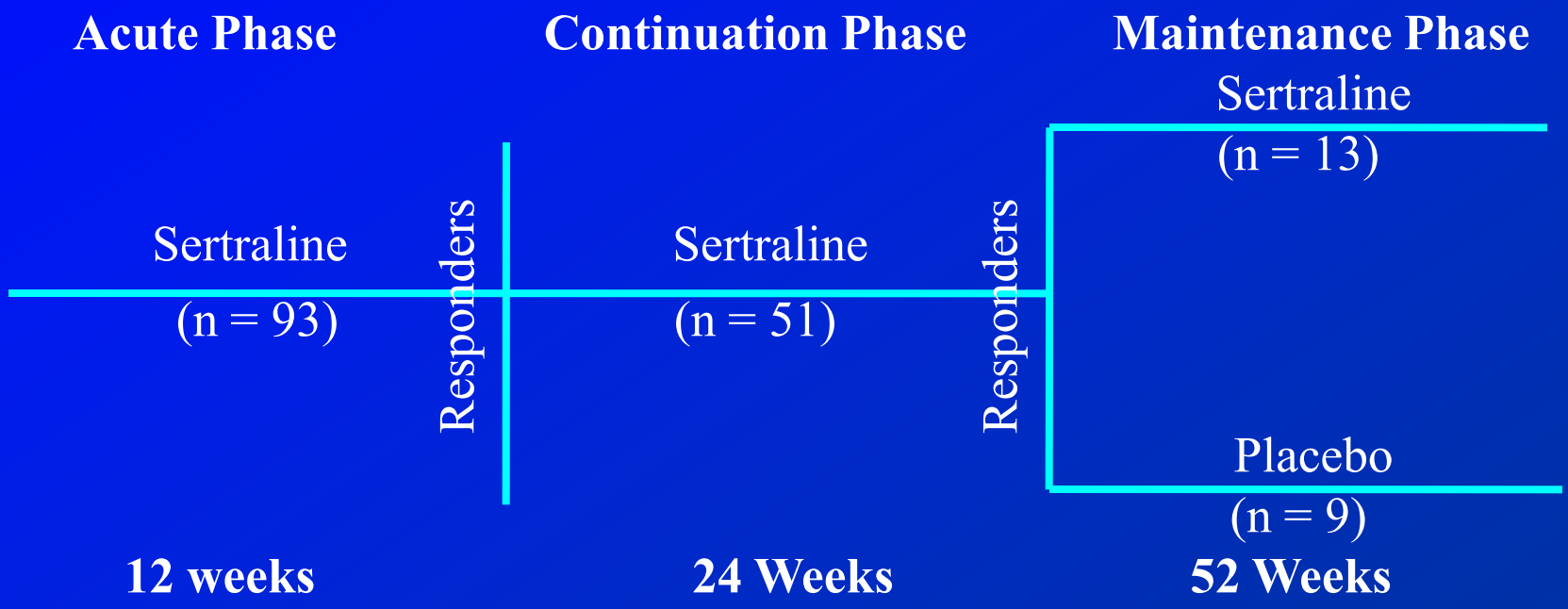


oxetine

- 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

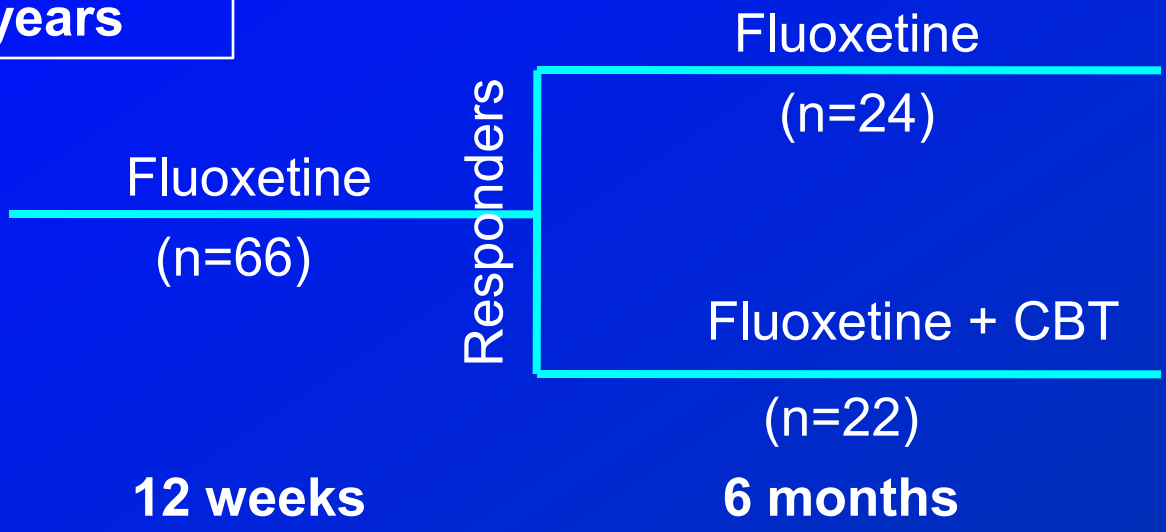


Maintained Response (No Recurrence) at 52 Weeks	
38%	Sertraline
0%	Placebo

Cheung et al, J Child Adolesc Psychopharmacology, 2008; 18:389-394

CBT to Prevent Relapse in Pediatric Depression

Ages 11-18 years



Relapse Rates at 6 Months (CDRS-R≥40 and 2 weeks symptom worsening or clinical deterioration)	
37%	Fluoxetine
15%	Fluoxetine + CBT

Kennard et al J Am Acad Child Adolesc Psychiatry 2008; 47:1395-1404

Box Warning on Antidepressants

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

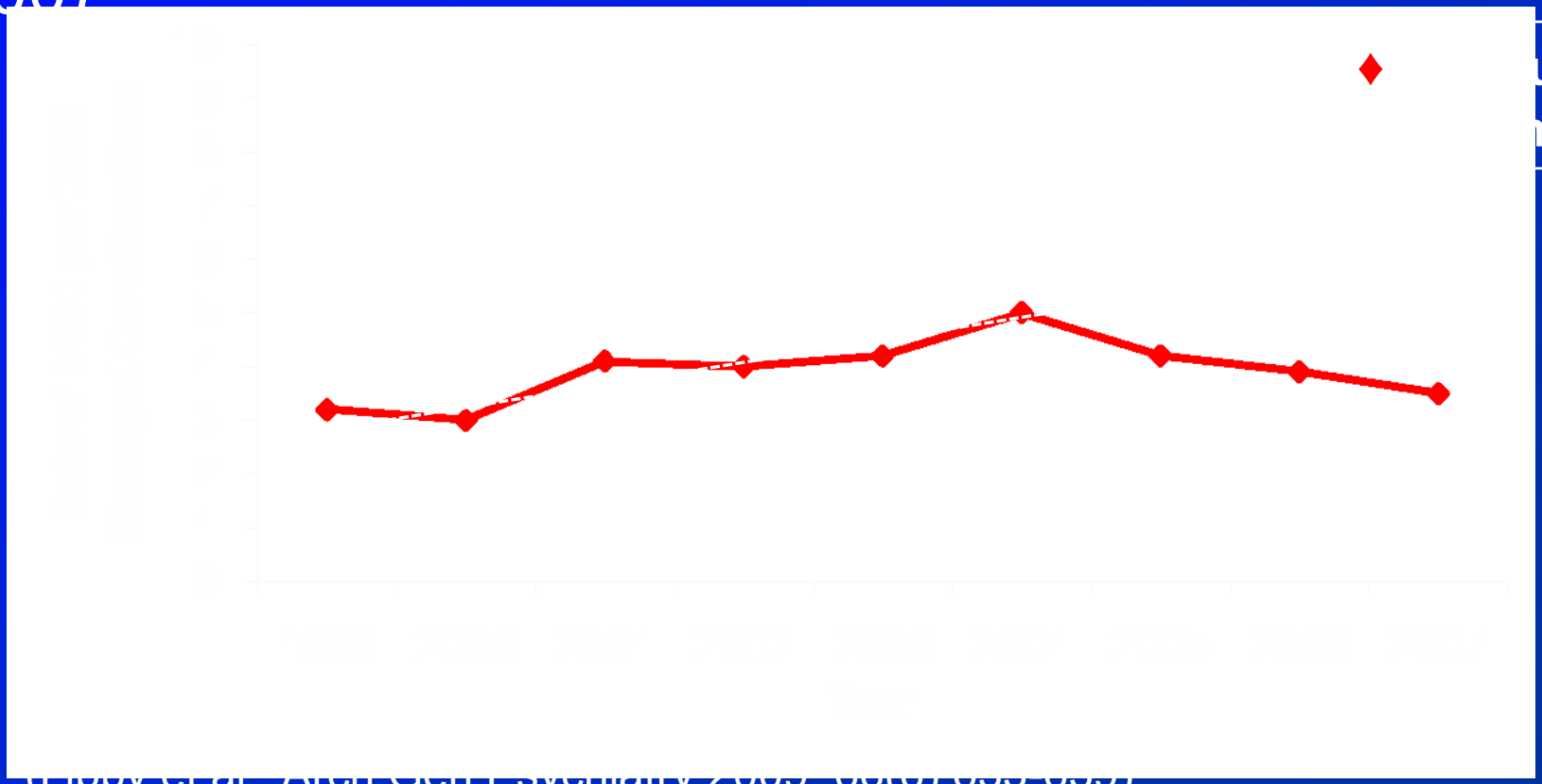
Revision

- 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



(Libby et al., Arch Gen Psychiatry 2009; 66(6):633-639)

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

Libby et al., Arch Gen Psychiatry 2009; 66(6):633-639

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	Suicidal Acts
SSRIs	
Citalopram	.97
Fluvoxamine	1.05
Paroxetine	.80
Sertraline	1.02
SNRIs	1.36
Tricyclics	.92

Schneeweiss et al Pediatrics 2010; 125:876-888

Efficacy vs. Suicidal Risk of Antidepressants in Pediatric Patients

- Meta-analysis of 27 trials of pediatric major depression

Number Needed to Treat	**10**
Number Needed to Harm	**112**

	Suicidal Ideation/attempts
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