Antidepressants in Childhood Depression: Boon or Bane?

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Disclosure

Objectives

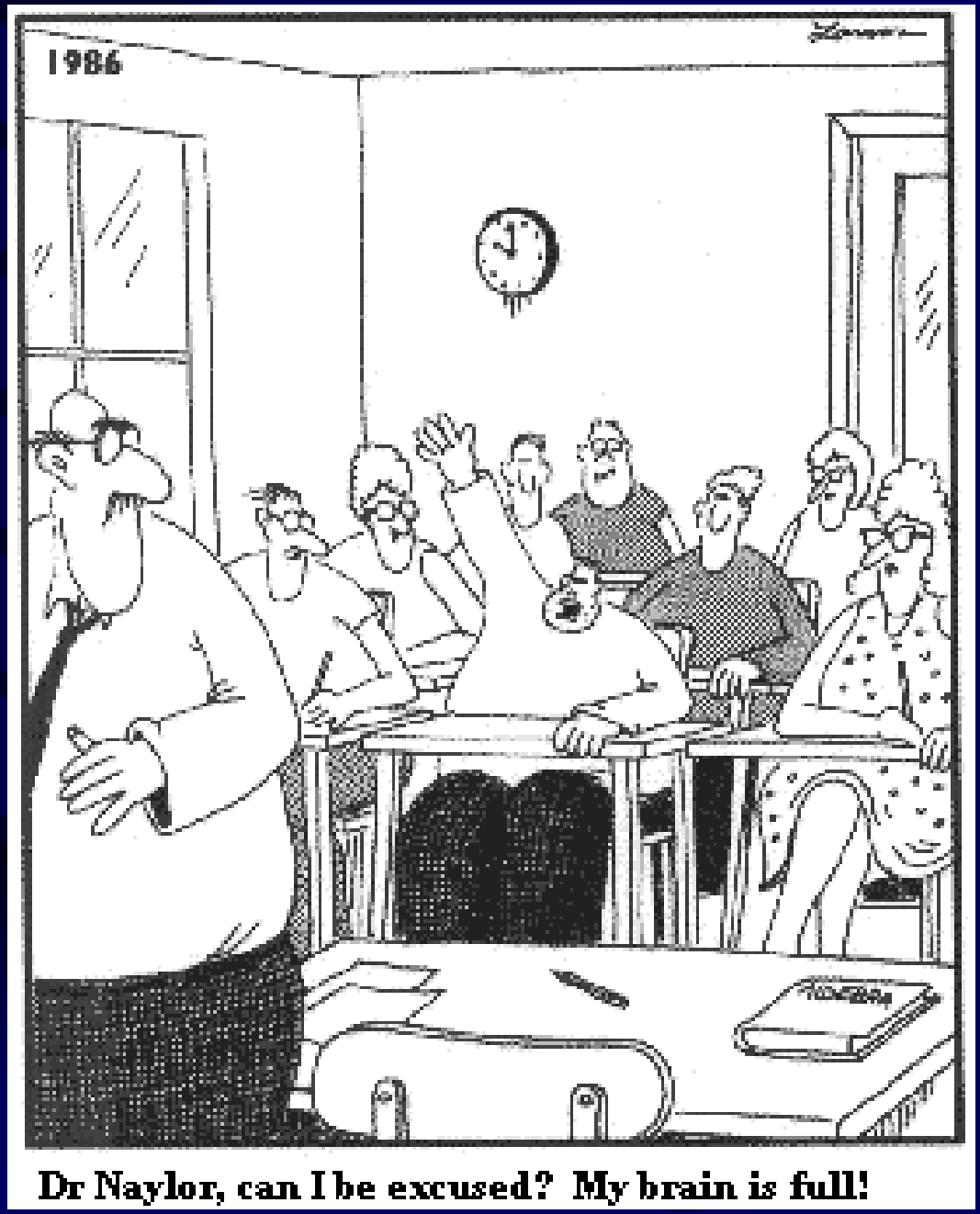
The participant will:

- **be able to compare the effectiveness and safety of the various antidepressants that have been used in treating pediatric depression.**
- **be familiar with the data relating antidepressants and suicidal behavior in children and adolescents.**

Objectives

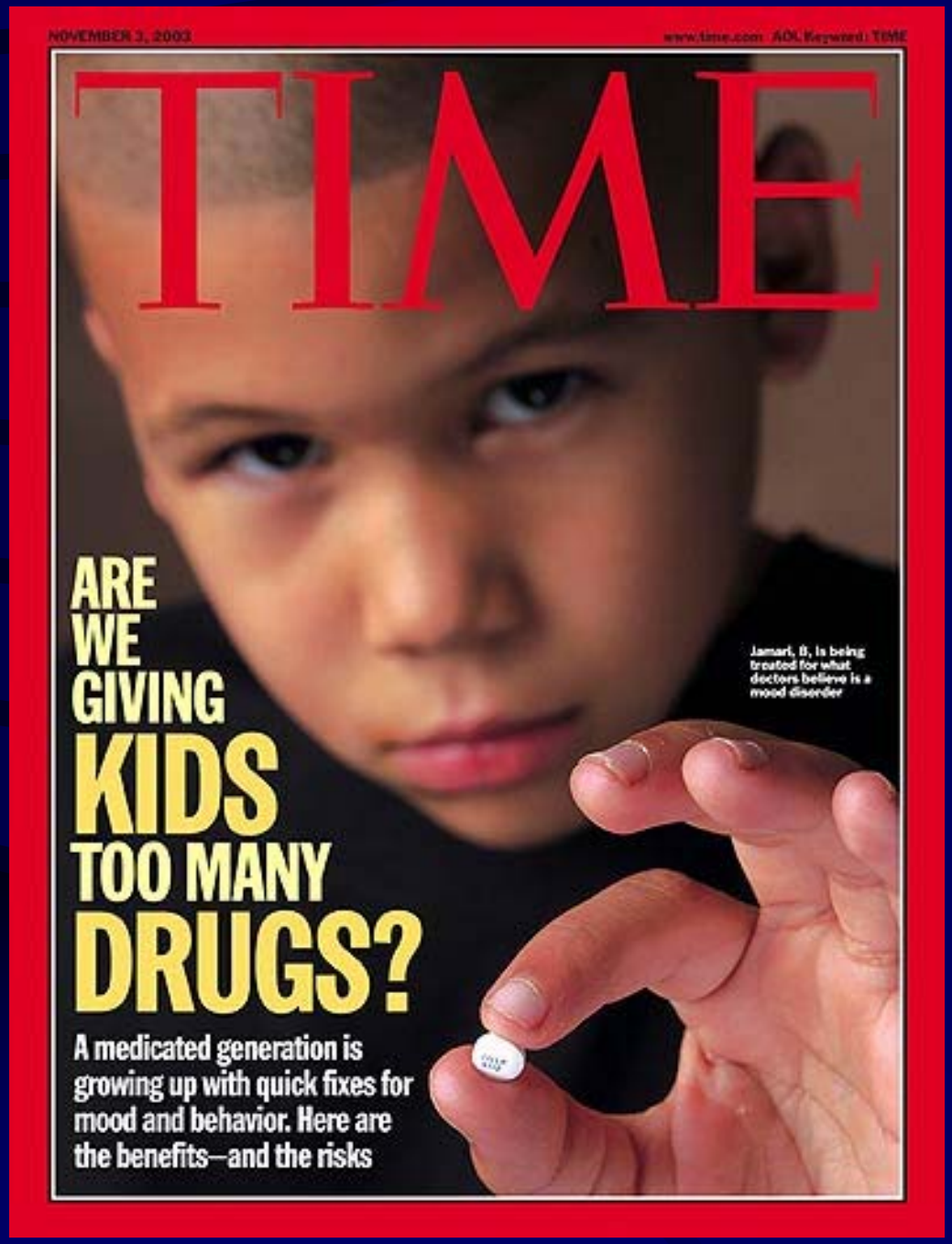
The participant will :

- **be familiar with the use of medication algorithms to guide the treatment of depression in childhood and adolescence.**


1986
Dr Naylor, can I be excused? My brain is full!

The Bottom Line

- Fluoxetine is the drug of choice for the treatment of childhood and adolescent depression.
- Children and adolescents being treated with antidepressants need to be monitored closely, especially early in the treatment.


NOVEMBER 3, 2003
www.time.com AOL Keyword: TIME
TIME
ARE WE GIVING KIDS TOO MANY DRUGS?
A medicated generation is growing up with quick fixes for mood and behavior. Here are the benefits—and the risks
Jamari, 8, is being treated for what doctors believe is a mood disorder

Teen gets 30 years in Zoloft case

Boy found guilty of murder in grandparents' deaths

From Jim Polk
CNN

Wednesday, February 16, 2005 Posted: 4:23 AM EST (0923 GMT)

CHARLESTON, South Carolina (CNN) -- A judge sentenced a 15-year-old boy Tuesday to 30 years in prison for killing his grandparents after jurors rejected defense arguments that taking the antidepressant Zoloft drove the youth to kill.

In this image from television, Pittman reacts as he is sentenced.

CNN.com

Prescription for suicide?

By MICHAEL D. LEMONICK SUNDAY, FEB. 01, 2004

Kara Jaye-Anne Otter, 12, had been on the antidepressant Paxil for seven months when she committed suicide. "I was told the worst side effects would be flu-like symptoms," recalls her mother, Shannon Baker. "But after three weeks she had begun to cop an attitude. Her grades started falling. Then she didn't care what she looked like, and she was fighting with everybody." Baker says her daughter developed rashes and dark circles under her eyes and had trouble sleeping. Then, on June 7, 2001, Kara pinned a note to her chest reading, "By the time you find me I'll be dead. I love you with all my heart. Don't worry, Jesus is with me." She hooked a bungee cord onto a plate hanger on the wall, wrapped the cord around her neck and pulled against it until she passed out. Within minutes she was dead.

Time

Family Wonders if Prozac Prompted School Shootings

Drug Dosage Grew Recently, Aunt Says

By MONICA DAVEY
and GARDINER HARRIS

RED LAKE, Minn., March 25 — In their sleepless search for answers, the family of Jeff Weise, the teenager who killed nine people and then himself, says it is left wondering about the drugs he was prescribed for his waves of depression.

On Friday, as Tammy Lussier prepared to bury Mr. Weise, who was her nephew and her father, who was among those he killed, she found herself looking back over the last year, she said, when Mr. Weise began taking the antidepressant Prozac after a suicide attempt that Ms. Lussier described as a "cry for help."

"They kept upping the dose for him," she said, "and by the end, he was taking three of the 20 milligram pills a day. I can't help but think it was too much, that it must have set him off."

Lee Cook, another relative of Mr. Weise, said his medication had increased a few weeks before the shootings on Monday.

"I do wonder," Mr. Cook said, "whether on top of everything else he had going on in his life, on top of all the other problems, whether the drugs could have been the final straw."

The effects of antidepressants on young people remain a topic of fierce debate among scientists and doctors.

Last year, a federal panel of drug experts said antidepressants could cause children and teenagers to become suicidal. The Food and Drug Administration has since required the makers of antidepressants to warn of that danger on their labels for the medications.

The suicide risk is particularly acute when therapy starts or a dosage changes, the drug agency has warned.

Although some studies link the drugs to an increased suicide risk, the research does not suggest such a connection to violence like Mr. Weise's rampage through Red Lake High School.

Without knowing Mr. Weise's medical history or precise diagnosis, it is

ter sitting there for what seemed like hours (which apparently was only minutes), I had the revelation that this was not the path."

"It was my dicision," he went on, "to seek medical treatment, as on the other hand I could've chose to sit there until enough blood drained from my downward lacerations on my wrists to die."

On Monday, in the hours before the shooting, Mr. Weise had seemed cheerful and normal, Ms. Lussier said. His teacher, who was spending an hour a day at his house as part of a "homebound" study program that the school system had created because of his troubles, arrived to give him his homework assignments, as usual. At 12:30 p.m., less than three hours before the shootings, another aunt, Shauna, stopped in.

"He was watching a movie on TV," Ms. Lussier said. "There was nothing out of the ordinary. People keep saying he was depressed, but if you saw him, he was getting better. All we can think of is, what about the drugs?"

Though research has not linked antidepressants to acts of violence on others, several incidents have gained wide publicity.

In 1989, Joseph Wesbecker walked

The New York Times

March 25, 2005

Antidepressants

- **Selective serotonin reuptake inhibitor (SSRIs):**
  - **fluoxetine (Prozac)**
  - **sertraline (Zoloft)**
  - **paroxetine (Paxil)**
  - **fluvoxamine (Luvox)**
  - **citalopram (Celexa)**
  - **escitalopram (Lexapro)**

Antidepressants

- **Atypical antidepressants**
  - **bupropion (Wellbutrin)**
  - **trazodone (Desyrel)**
  - **venlafaxine (Effexor)**
  - **nefazodone (Serzone)**
  - **mirtazapine (Remeron)**
  - **duloxetine (Cymbalta)**

Antidepressants

- **Tricyclic antidepressants (TCAs):**
  - **imipramine (Tofranil)**
  - **desipramine (Norpramin)**
  - **nortriptyline (Pamelor)**
  - **amitriptyline (Elavil)**
  - **clomipramine (Anafranil)**
  - **protriptyline (Vivactyl)**
  - **trimipramine (Surmontil)**
  - **doxepin (Sinequan, Adapin)**

Antidepressants

- **Monoamine oxidase inhibitors (MAOIs):**
  - **tranylcypromine (Parnate)**
  - **phenelzine (Nardil)**
  - **selegiline (EMSAM, Eldepryl, Zelapar)**

Show Me The Data!

Imipramine RCTs

Study	# of pts	Age	Findings
Keller et al. (2001) Paroxetine vs IMI vs plac	275	12 - 18	NS % < HAM-D 8 or > 50% ΔHAM-D
Puig-Antich et al. (1987)	38	9 (mean)	NS K-SADS depression response (56% vs 68%)*
Hughes et al. (1990)	31	6 - 12	NS CDRS-R

* - IMI + DMI correlated with antidepressant response

Desipramine RCTs

Study	# of pts	Age	Findings
Klein et al. (1998)	45	7 - 17	NS HAM-D
Boulous et al. (1991)	30	15 - 20	NS HAM-D response (50% vs 33%)
Kutcher et al. (1994)	60	15 - 19	NS HAM-D BDI

Amitriptyline RCTs

Study	# of pts	Age	Findings
Birmaher et al. (1998)	27	12 - 18	NS HAM-D
Kashani et al. (1984)	9	9 - 12	NS BID
Kye et al. (1996)	31	15 - 19	NS HAM-D ∆CGI severity

Nortriptyline RCTs

Study	# of pts	Age	Findings
Geller et al. (1990)	35	12 - 17	NS K-SADS depression
Geller et al. (1992)	50	9 - 12	NS CDRS-R KGAS K-SADS depression
Kye et al. (1996)	31	15 - 19	NS HAM-D ∆CGI severity

Fluoxetine RCTs

Study	# of pts	Age	Findings
Simeon et al. (1990)	40	13 - 18	NS
Emslie et al. (1997)	96	7 - 17	Flx > plac CGI - (56% vs 33%) CDRS-R total after 5 weeks
Emslie et al. (2002)	219	8 - 17	Flx > plac ∆ CDRS-R after 1 week ∆ CGI - severity
TADS Study (2004)	221	12 - 17	CDRS-R Flx + CBT > plac Flx > plac Flx > CBT

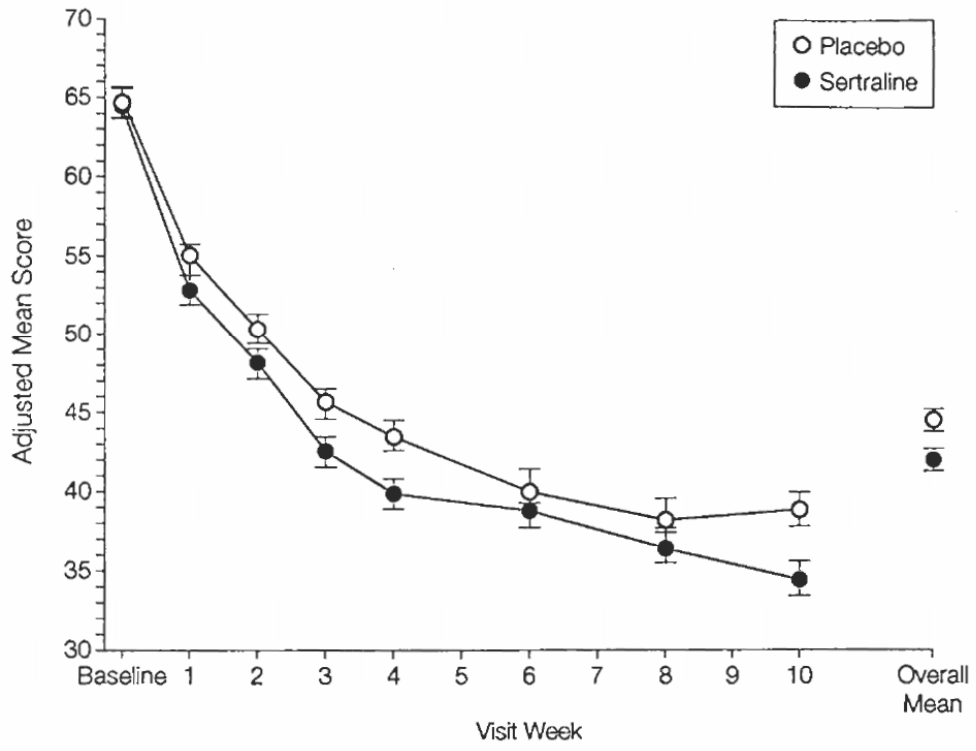
Sertraline RCTs

Study	# of pts	Age	Findings
A0501001*	188	6 - 17	ΔCDRS-R, p = 0.08 % CDRS-R response, NS
A0501017*	185	6 - 17	ΔCDRS-R, NS % CDRS-R response p = 0.03
Wagner et al. (2003)* Sertraline	376	6 - 17	SRT > plac Δ CDRS-R: -22.85 vs -20.19 > 40% decrease 69% vs 59%

*Two studies: pooled results were positive; individually - 1 positive trend, 1 negative

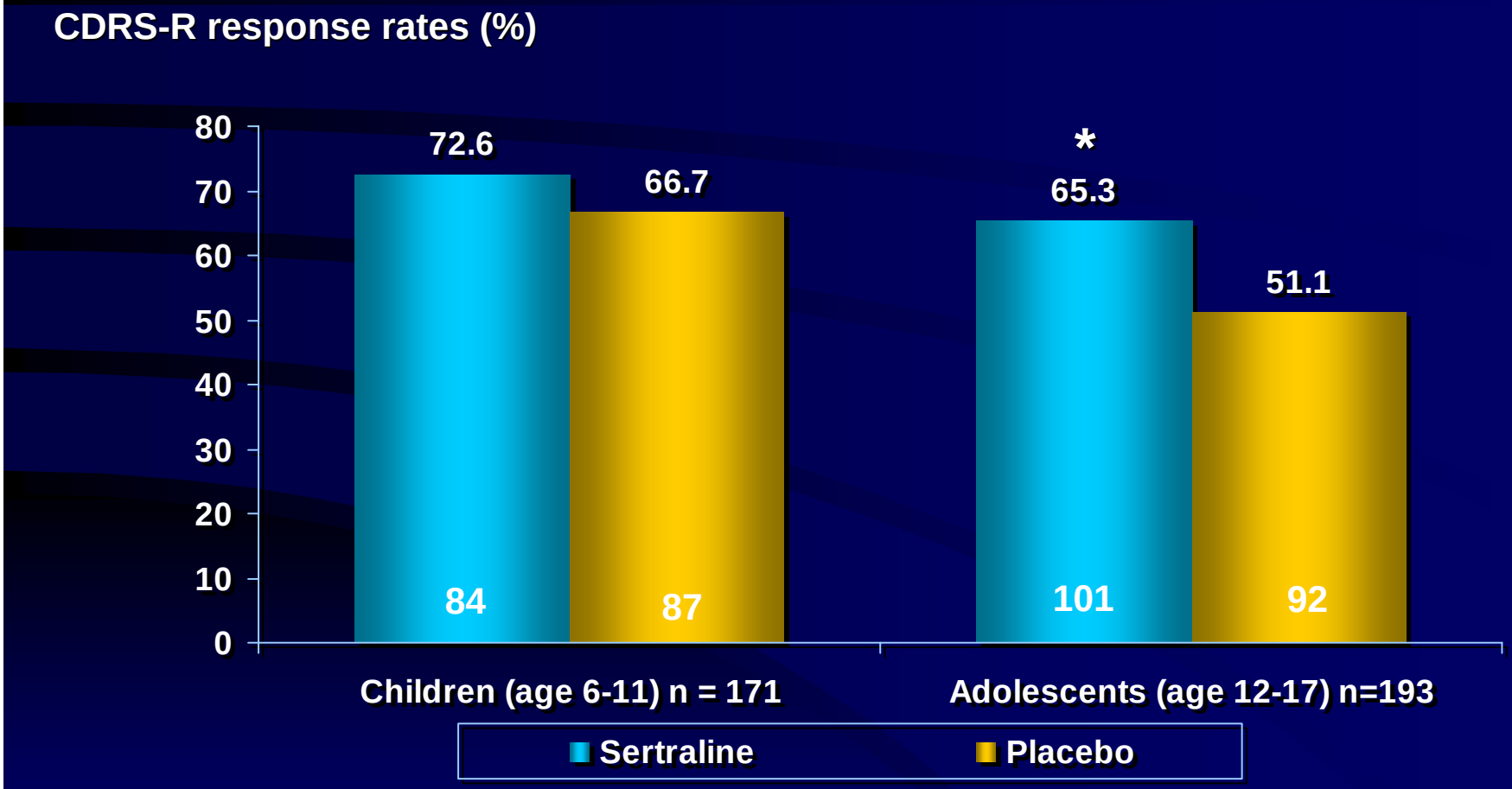
Sertraline vs Placebo

Figure 2. Weekly and Overall Adjusted Mean CDRS-R Scores



Wagner et al., 2003

CDRS-R Response Rates in Children vs Adolescents



*p<0.05
Response rate defined as a ≥40% decrease on CDRS total score from baseline

Paroxetine RCTs

Study	# of pts	Age	Findings
Emslie et al. (2006) Paroxetine	206	7 - 17	NS CDRS-R CGI
Berard et al. (2006) Paroxetine	286	13 - 18	NS MADRS KSADS-L depression scale
Keller et al. (2001) Paroxetine vs IMI vs plac	275	12 - 18	NS % < HAM-D 8 or > 50% ∆HAM-D

Imipramine vs Paroxetine vs Placebo

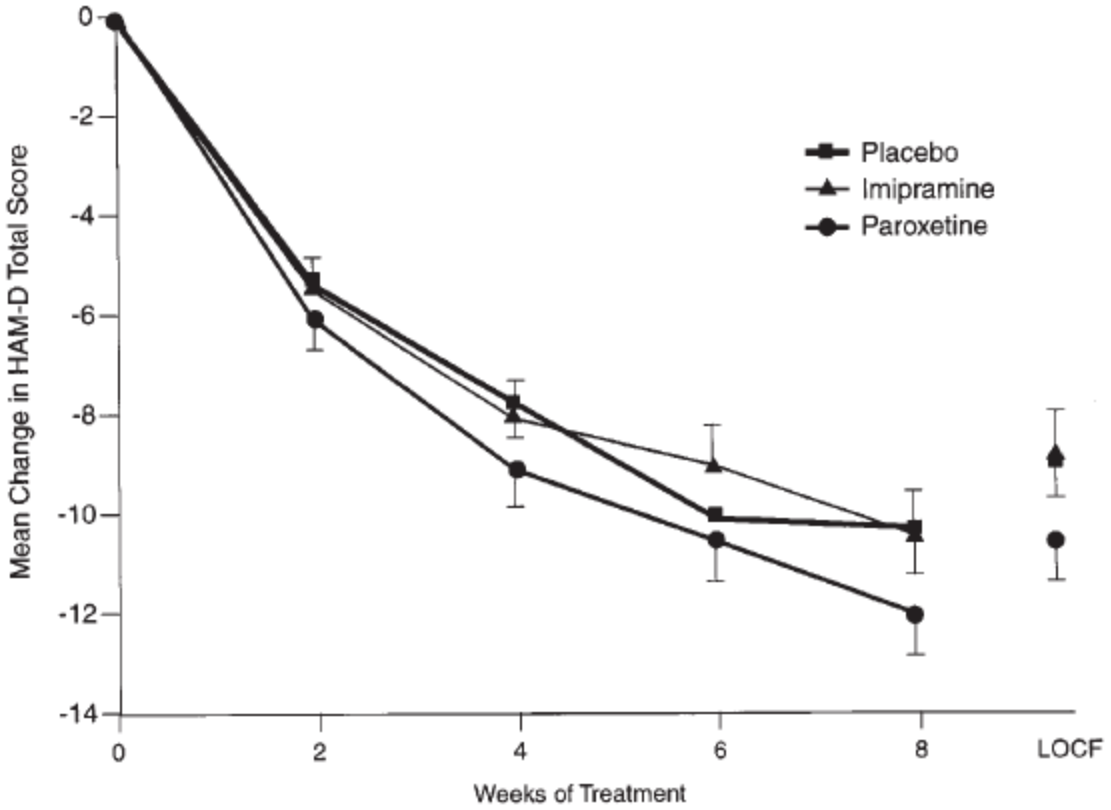
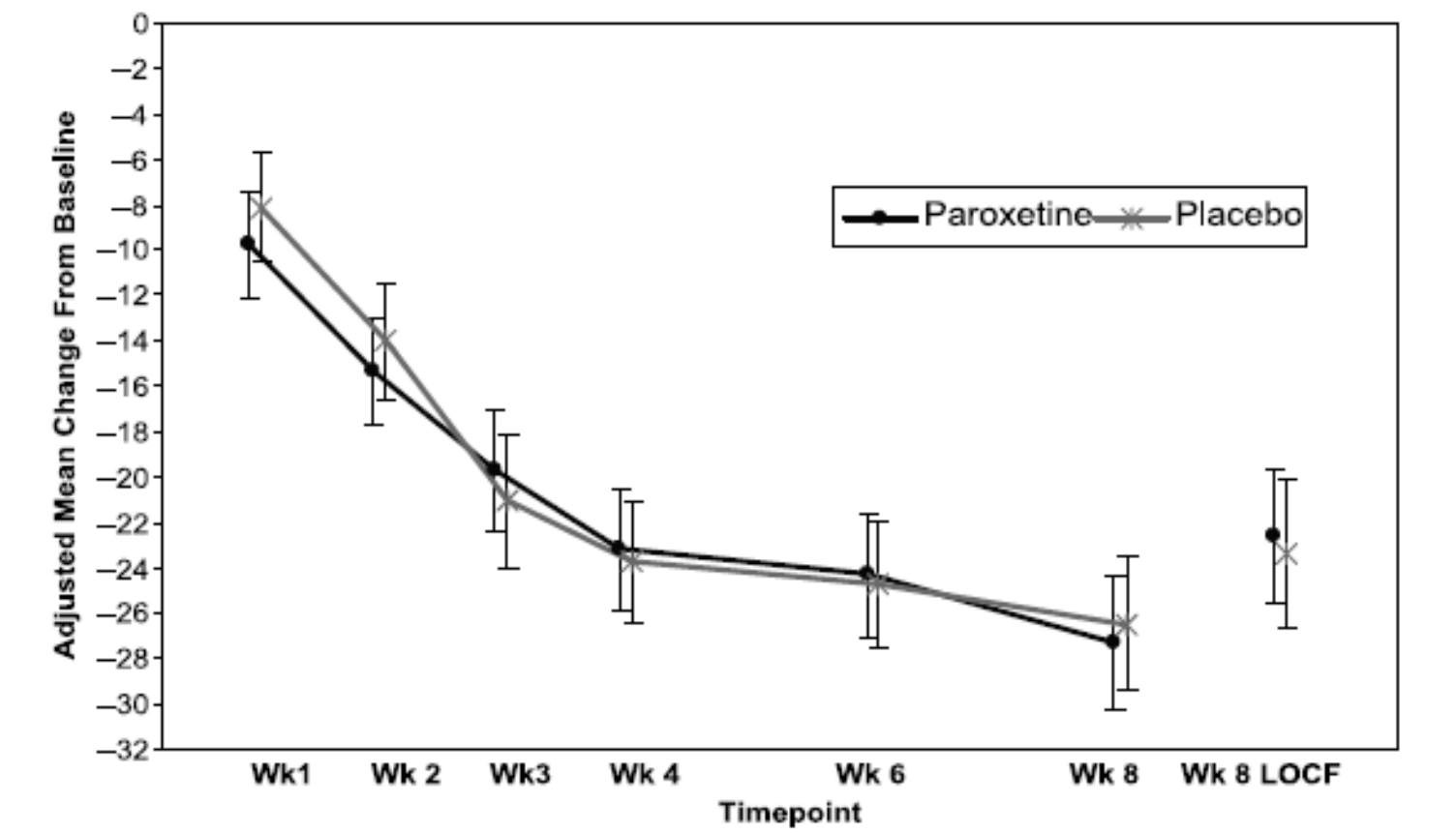


Fig. 2 Least square mean change HAM-D total score (±SEM) during an 8-week course of paroxetine (n = 90), imipramine (n = 94), and placebo (n = 87) administration in adolescents with major depression. HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward.

Paroxetine vs Placebo



Emslie et al., 2006

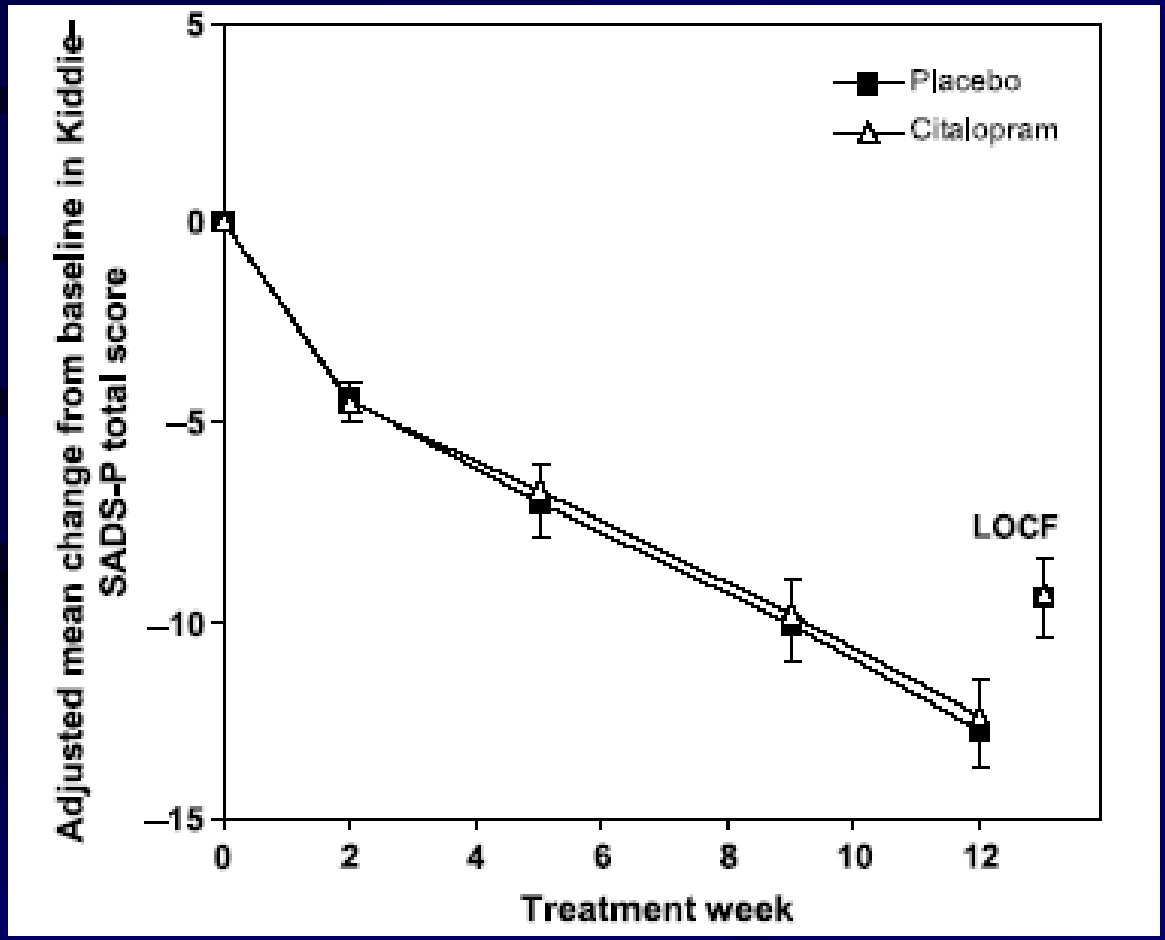
Paroxetine vs Placebo

Berard et al., 2006

Citalopram RCTs

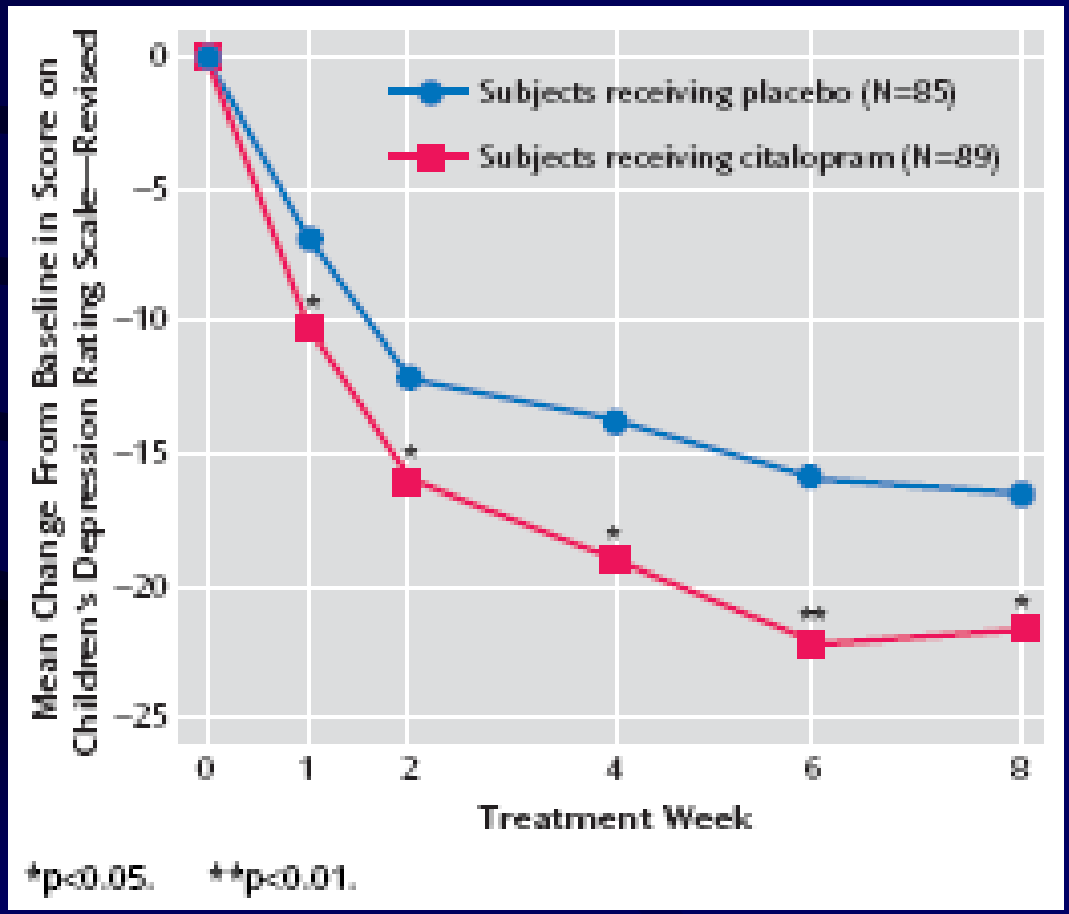
Study	# of pts	Age	Findings
von Knorring et al. (2006) Citalopram	244	13 - 18	NS K-SADS-P depression scale MADRS
Wagner et al. (2004) Citalopram	174	7 - 17	CTP > plac ∆CDRS – R after 1 week Responders: 36% vs 24%
Wagner et al. (2006) Escitalopram	219	8 - 17	NS For adolescents ESC > plac: CGI – S, CGI - I, CGAS (LOCF)

Citalopram vs Placebo



von Knorring et al., 2006

Citalopram vs Placebo



Wagner et al., 2004

Venlafaxine RCTs

Study	# of pts	Age	Findings
FDA - 382*	161	7 - 17	NS ΔCDRS-R (-18.1 vs -16.1)
FDA - 394*	193	7 - 17	NS ΔCDRS-R (-24.3 vs -22.6)
Emslie et al. (2007)*	334	7 - 17	NS For adolescents VLF > plac ΔCDRS-R (-24.4 vs -19.9) CDRS-R response (71% vs 55%)
Mandoki et al. (1997)	33	8 - 17	NS CDRS-R

* – pooled data

Nefazodone RCTs

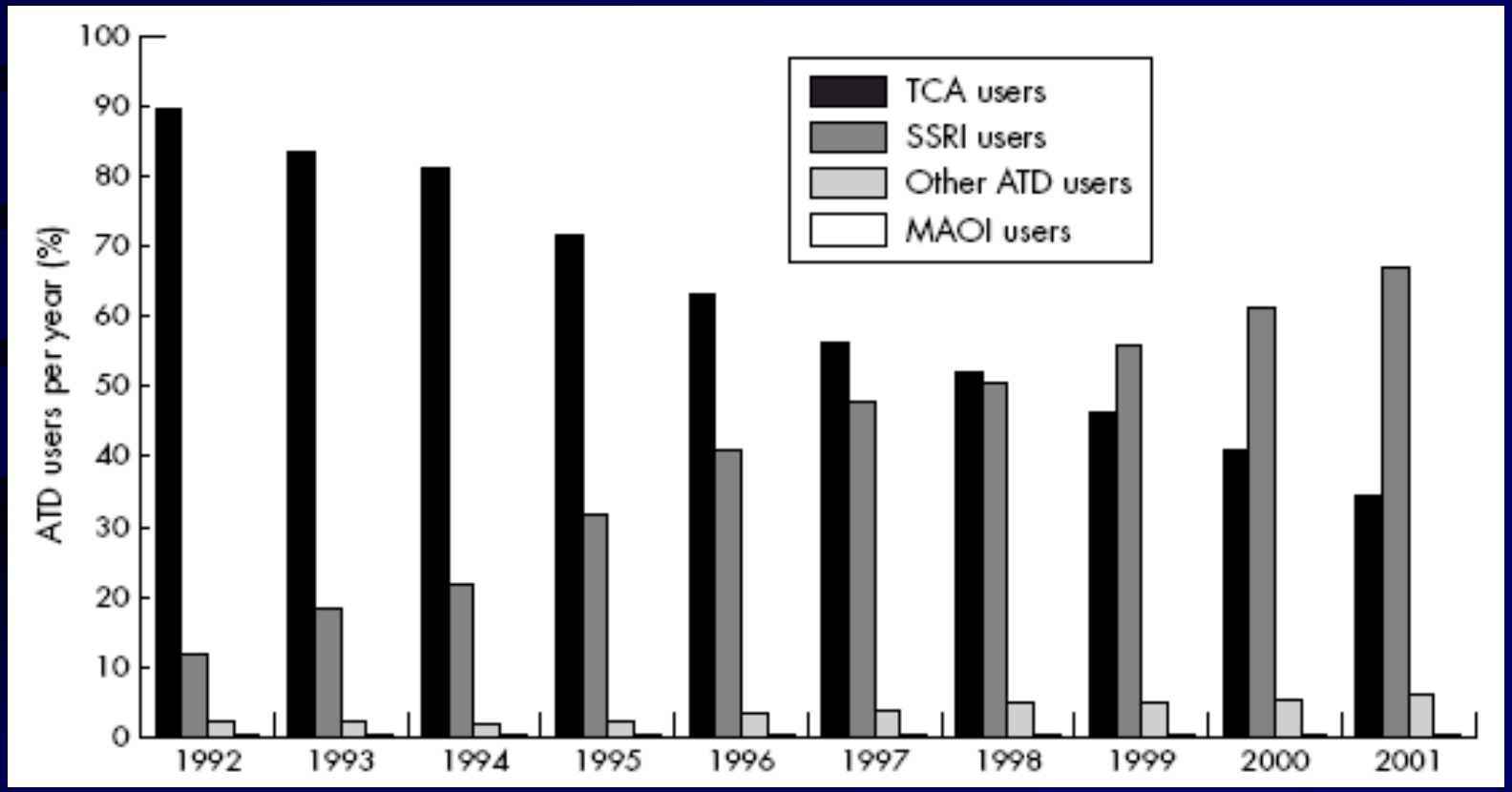
Study	# of pts	Age	Findings
FDA – 187*	278	7 - 17	NS ΔCDRS-R
FDA – 141*	201	12 - 17	NS ΔCDRS-R (-25.8 vs -22.1, NS) CGI response (63% vs 44%)
Emslie et al. (2002)*	195	12 - 17	NEF > plac ΔCDRS-R (-26.5 vs -22.5, NS) CGI response (62% vs 42%)

* – same study presented at different time points

Mirtazepine RCTs

Study	# of pts	Age	Findings
003-045 Study 1	126	7 - 17	NS CDRS-R GGI response
003-045 Study 2	133	7 - 17	NS CDRS-R GGI response

Antidepressant Prescriptions in Children and Adolescents

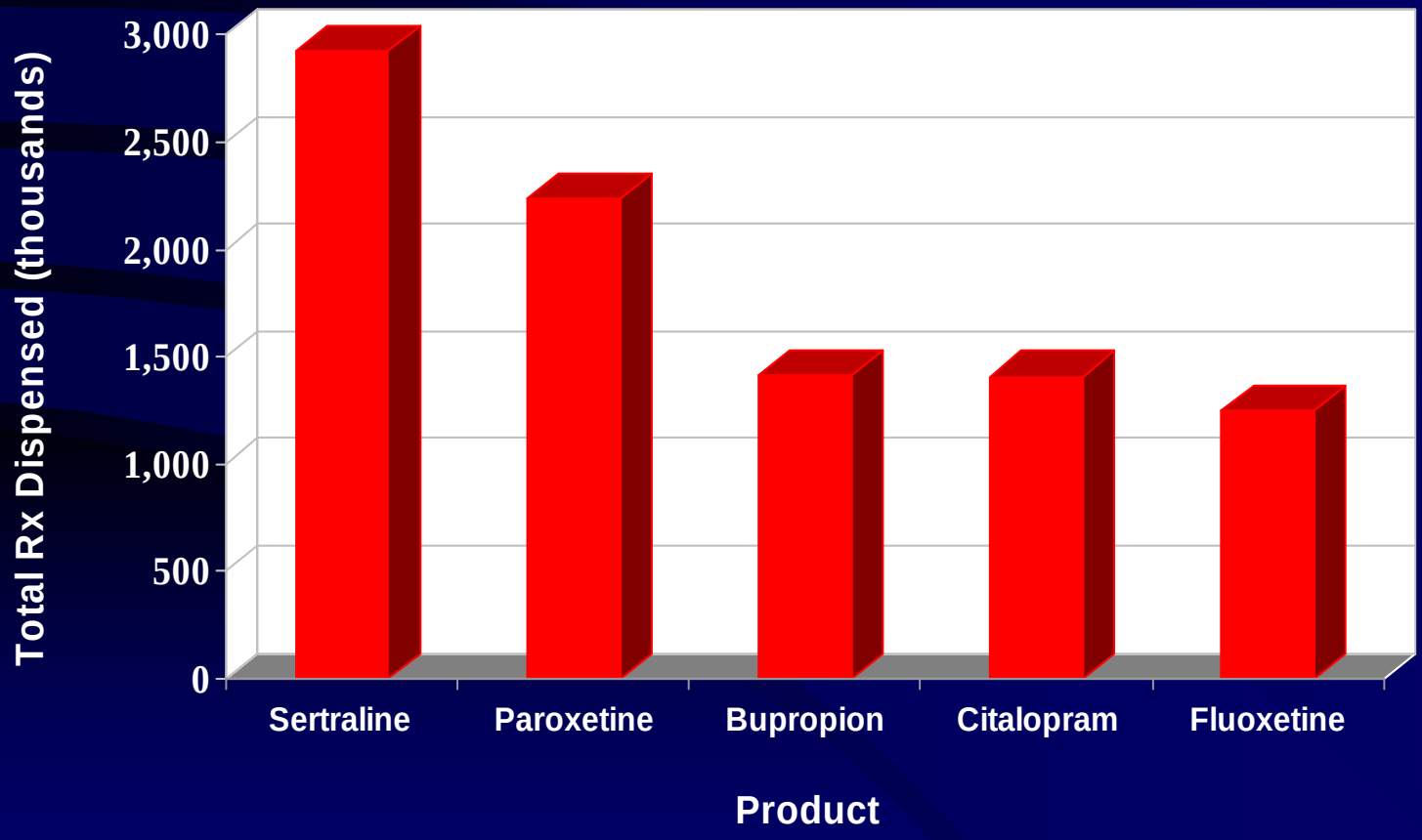


Murray et al., 2004

Efficacy of Antidepressants for Pediatric Depression

- **Randomized controlled trial results submitted to the FDA for pediatric depression:**
  - **fluoxetine: 3 out of 3 trials positive**
  - **all other antidepressants combined: 1 out of 14 trials positive**

Top 5 Antidepressants Dispensed to 1 - 17 Year Olds



National Prescription Audit Plus™; National Disease and Therapeutic Index™ ; 1998 - 2002

What Are The Safety Concerns?

Medicines and Healthcare Products Regulatory Agency Statement

- **“Only fluoxetine (Prozac) was shown in clinical trials to have a positive balance of risks and benefits for the treatment of depressive illness in under 18’s.”**
- **“For depressive illness, paroxetine, venlafaxine, sertraline, escitalopram and citalopram are contraindicated. Contraindication means that a medicine should not be used but not that it cannot be used.”**

12/10/2003

FDA Warning

- The Food and Drug Administration (FDA) added a warning statement to the labeling of ten antidepressants for worsening depression or the emergence of suicidality. The drugs include: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine)

3/22/2004

Risk Estimates of Definitive Suicidal Behavior/Ideation

Drug	Relative Risk (95% CI), all trials, all indications	Relative Risk (95% CI), MDD trials
Prozac	0.92 (0.39, 2.19)	0.89 (0.36, 2.19)
Paxil	2.65 (1.00, 7.02)	2.15 (0.71, 6.52)
Zoloft	1.48 (0.42, 5.24)	2.16 (0.48, 9.62)
Celexa	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Effexor	4.97 (1.09, 22.72)	8.84 (1.12, 69.51)
Remeron	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)

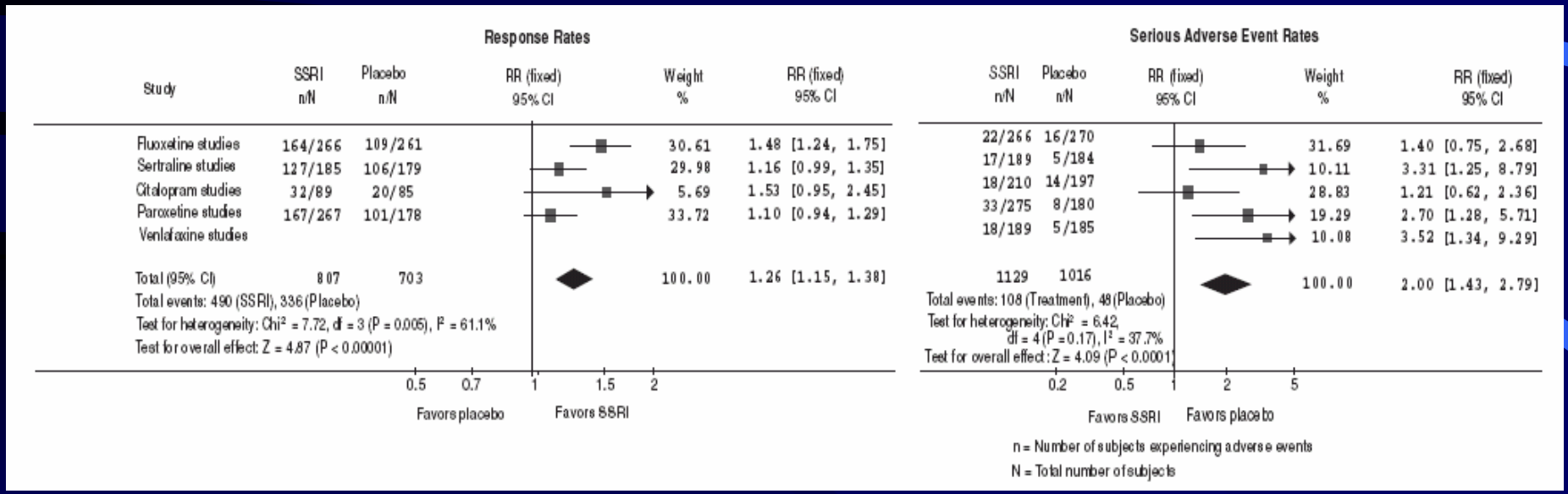
FDA's analysis of Columbia University's reclassification of adverse events, Tarek Hammad, 2004

Risk Estimates of Treatment-Emergent Agitation or Hostility

Drug	Relative Risk (95% CI), MDD trials
Prozac	1.01 (0.40, 2.55)
Paxil	7.69 (1.80, 32.99)
Zoloft	2.92 (0.31, 27.83)
Celexa	1.87 (0.34, 10.13)
Effexor	2.86 (0.78, 10.44)
Remeron	0.52 (0.03, 8.27)
Serzone	1.09 (0.53, 2.25)

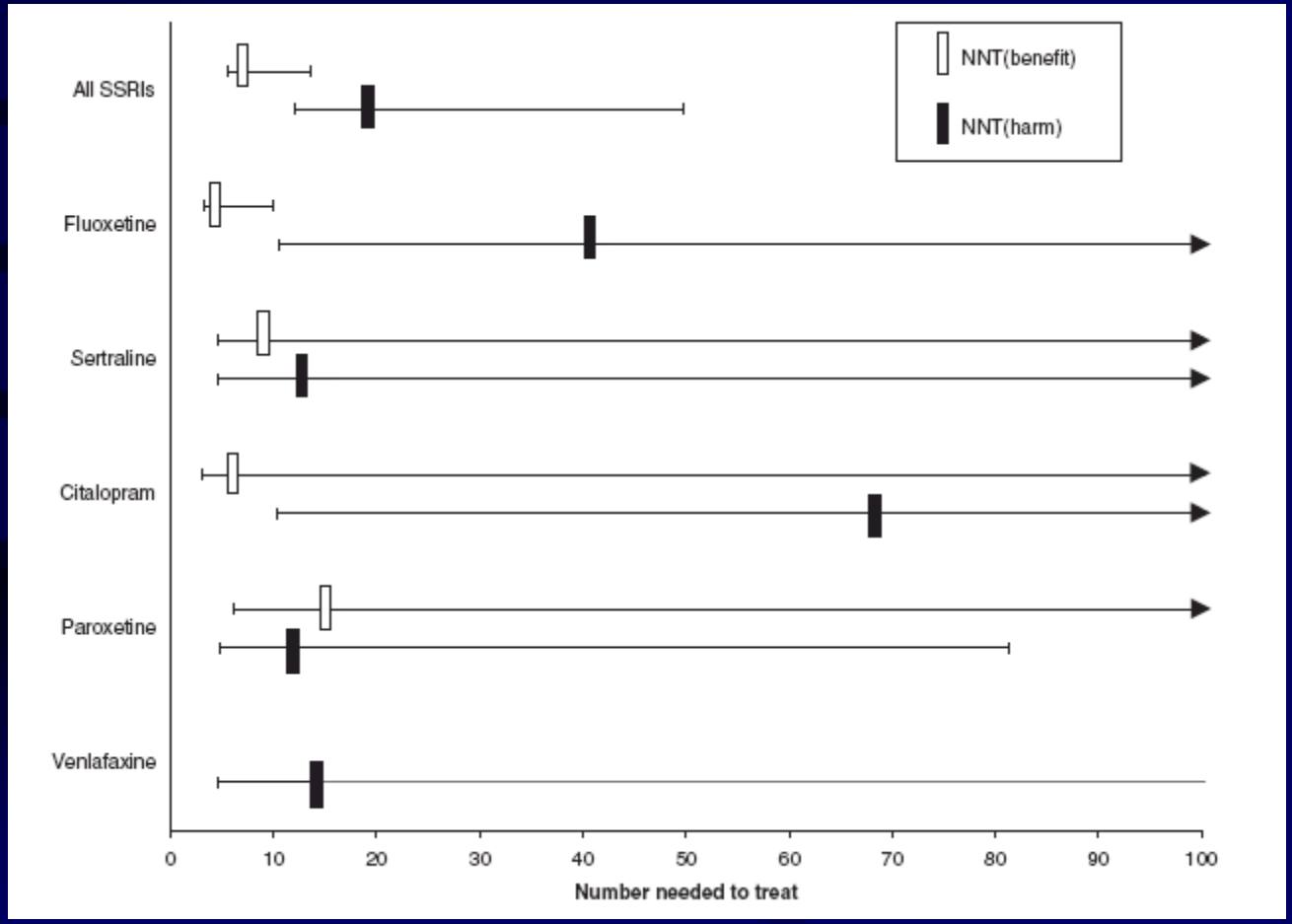
FDA's analysis of Columbia University's reclassification of adverse events, Tarek Hammad, 2004

Risks and Benefits for SSRIs



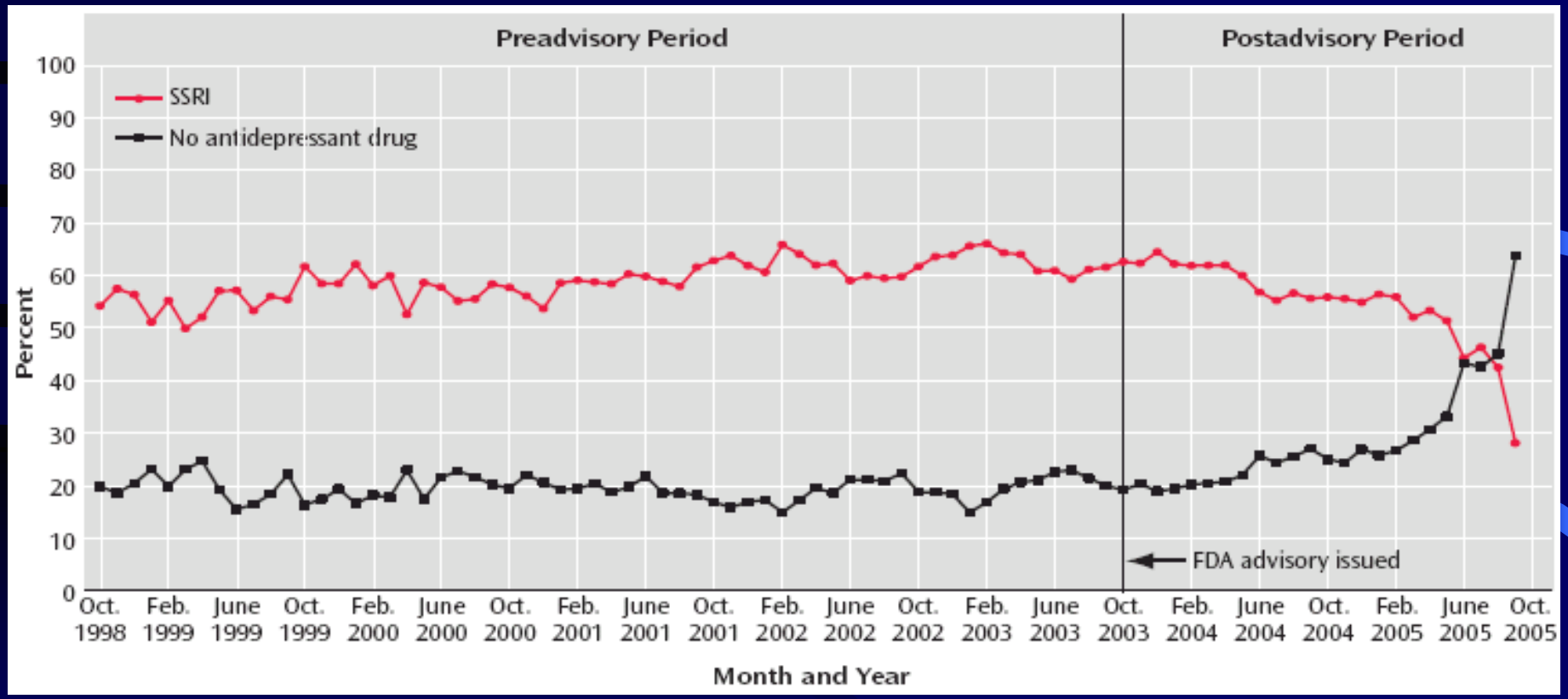
Wallace et al., J Child Adol Psychopharm, 2006

Risks and Benefits for SSRIs



Wallace et al., J Child Adol Psychopharm, 2006

Decline in Prescription of SSRIs After FDA Warning



Libby et al., Am J Psychiatry, 2007

Suicide Risk with Antidepressant Treatment

- Relative risk of suicide attempt and death in severely depressed children and adults treated with antidepressant drugs
- Medicaid beneficiaries
- Patients aged 6 – 64 treated at one time on an inpatient unit for depression
- matched for age, sex, race or ethnicity, substance use, recent suicide attempt

Olfson, et al., 2006

Suicide Risk with Antidepressant Treatment

- For adults (aged 19-64 years), antidepressant treatment was not associated with suicide attempts or deaths
- antidepressant drug treatment was significantly associated with suicide attempts (OR, 1.52) and suicide deaths (OR, 15.62) for children and adolescents

Olfson,et al., 2006

Suicide Risk with Antidepressant Treatment

• Any SSRI	OR=1.24
– fluoxetine (Prozac)	OR=0.69
– paroxetine (Paxil)	OR=1.36
– sertraline (Zoloft)	OR=1.88
– citalopram (Celexa)	OR=0.68
– fluvoxamine (Luvox)	OR=0.91
– tricyclic antidepressants	OR=3.09
– venlafaxine (Effexor)	OR=2.33
– mirtazapine (Remeron)	OR=1.64
– bupropion (Wellbutrin)	OR=1.07
– trazodone (Desyrel)	OR=0.86
– nefazodone (Serzone)	OR=1.62

Olfson,et al., 2006

Risk for Suicide Related Behavior

Table 6. Summary of Associations of Suicide Attempts and Completion With Antidepressant Drug Treatment in Depressed Medicaid Patients

Group	Participants, %*		*P* Value†	Odds Ratio (95% CI)
	Cases	Controls		
Adults, 19-64 y				
Suicide attempts	(n = 521)	(n = 2394)		
No antidepressant drugs	53.2	55.9		1.00
Any antidepressant drug	46.8	44.1	.46	1.10 (0.86-1.39)
SSRI	26.1	25.0	.72	0.97 (0.72-1.30)
Suicide completions	(n = 86)	(n = 396)		
No antidepressant drugs	46.5	45.2		1.00
Any antidepressant drug	53.5	54.8	.70	0.90 (0.52-1.55)
SSRI	29.1	30.0	.83	0.87 (0.44-1.73)
Children, 6-18 y				
Suicide attempts	(n = 263)	(n = 1241)		
No antidepressant drugs	54.4	63.9		1.00
Any antidepressant drug	45.6	36.1	.007	1.52 (1.12-2.07)
SSRI	29.7	25.5	.21	1.24 (0.86-1.79)
Suicide completions	(n = 8)	(n = 39)		
No antidepressant drugs	50.0	87.2		1.00
Any antidepressant drug	50.0	12.8	.002	15.62 (≥1.65)‡
SSRI	37.5	7.7	.005	11.26 (≥0.97)‡

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.
*Controls were matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.
†By Cochran-Mantel-Haenszel χ^2 test.
‡Exact conditional logistic regression.

Olfson et al, 2006

PHARMO Data

- Nationally representative sample of 2,000,000 people in the Netherlands
- Complete medical records for 10 years
  - study period: 1998 – 2005
  - ages < 15 and 15 – 19 years
  - M and F

Gibbons, Report to FDA

PHARMO Data

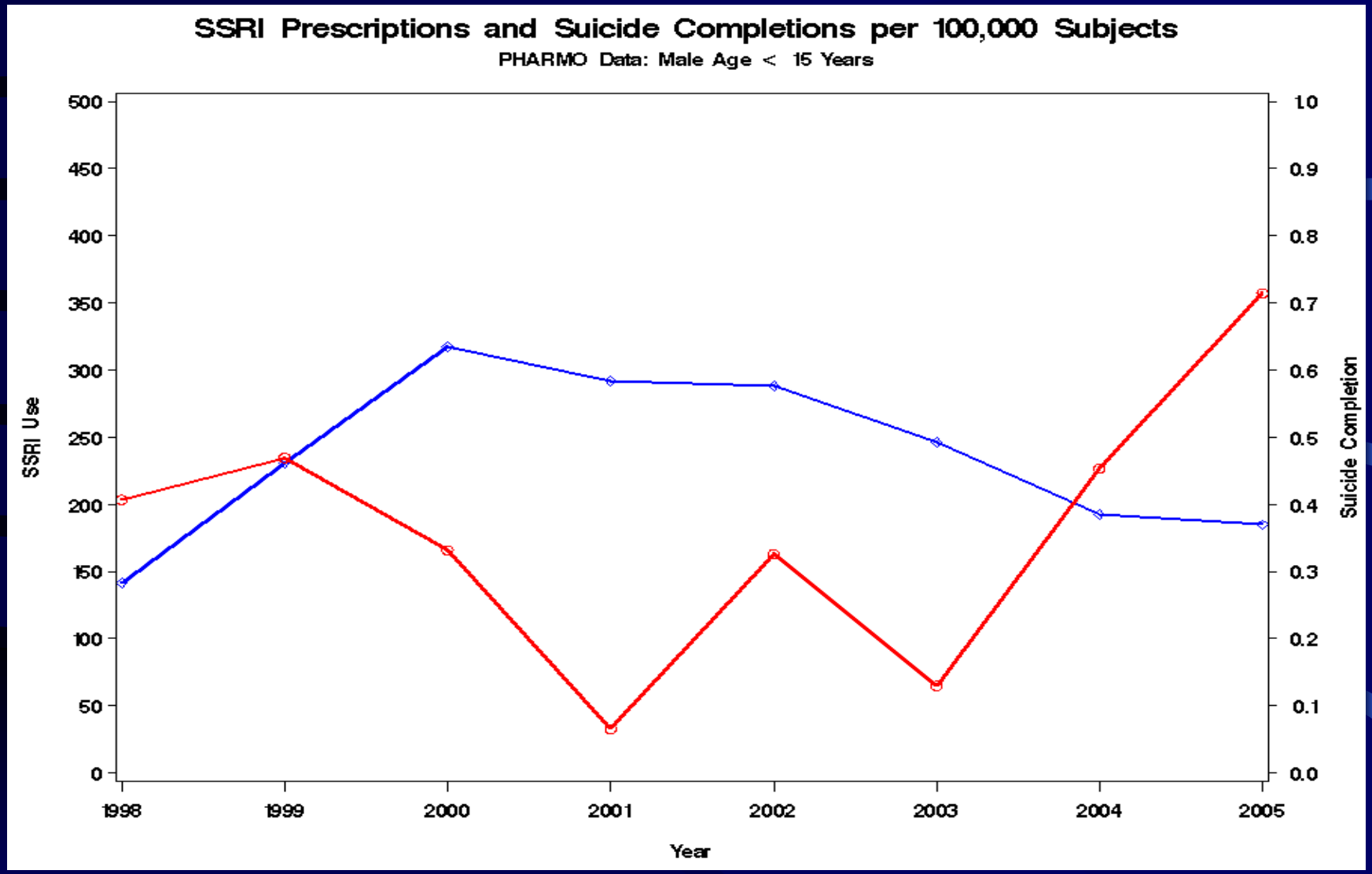
- 1998 – 2005
  - Significant inverse association between SSRI prescriptions and youth suicide rates overall ($p<.04$)
  - Strongest effect for boys < 15, $r = -.67$, $p<.05$.

Gibbons, Report to FDA

PHARMO Data

- 2003 – 2005
  - 22% decrease in youth SSRI prescriptions
  - 49% increase in youth suicide
  - 446% increase in youth suicide for boys < 15

Gibbons, Report to FDA



Gibbons, Report to FDA

U.S. Model Predictions

- **Total Population**
  - **30% reduction in SSRI+NSSRI**
  - **increase of 1.8 suicides per 100,000**
  - **or 5517 completed suicides per year.**
- **Children and young adolescents 5-14**
  - **30% reduction in SSRI+NSSRI**
  - **increase of 0.20 suicides per 100,000**
  - **or 81 completed suicides per year**

Gibbons, Report to FDA

Suicide Risk with Antidepressant Treatment

- To evaluate relationship between regional changes in antidepressant treatment and suicide rates
  - 1990 - 2000
  - Ages 10 – 19 years

Olfson et al., Arch Gen Psych, 2003

Suicide Risk with Antidepressant Treatment

- **Results:**
  - **significant negative relationship between rate of antidepressant prescription and suicide**
  - **a 1% increase in antidepressant use was associated with a decrease in suicide rate of 0.23 suicides/100,000 adolescents/yr**
  - **this finding did not hold for tricyclic antidepressants**

Olfson et al., Arch Gen Psych, 2003

Antidepressant Prescription Rates and Rate of Adolescent Suicide

- National county-level suicide rate data
- National county-level antidepressant prescription rate - number of pills prescribed per person
  - children ages 5–14
  - 1996–1998

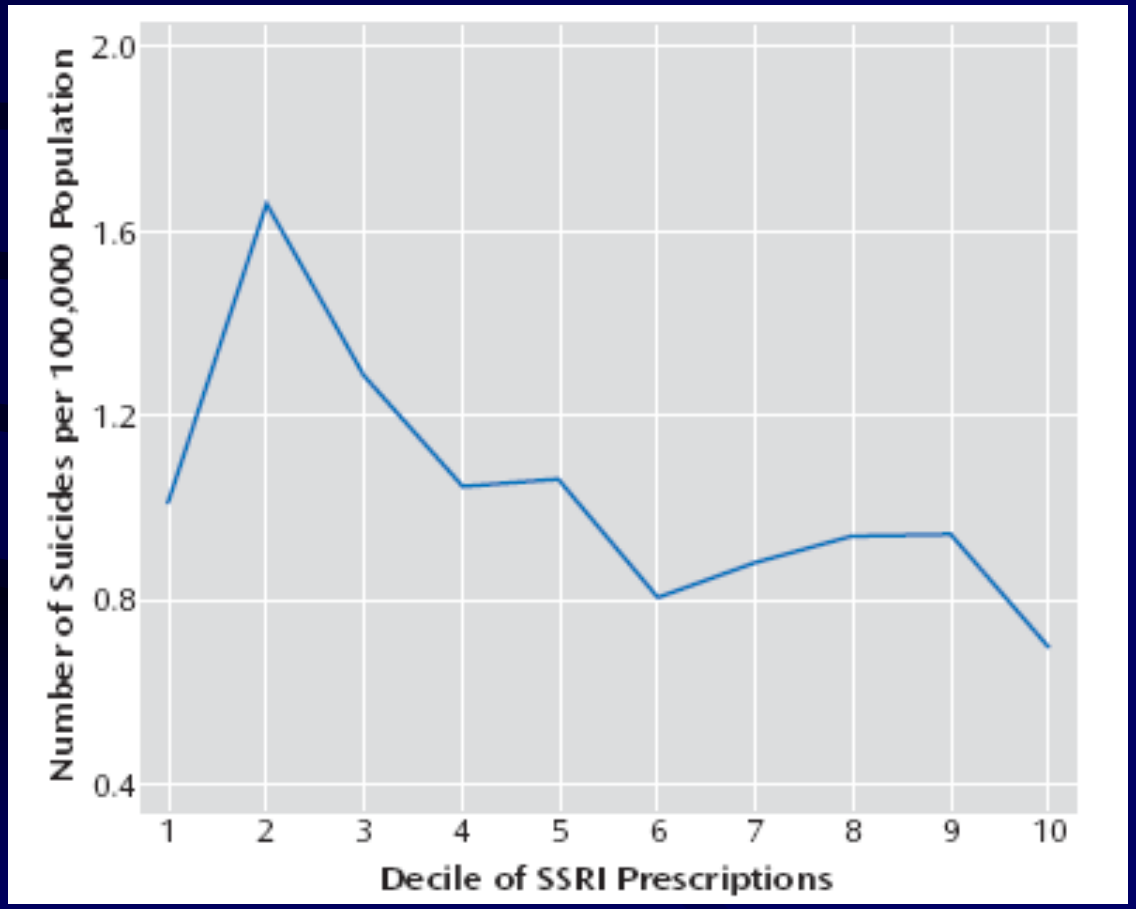
Gibbons et al., Am J Psychiatry 163:11, 2006

Antidepressant Prescription Rates and Rate of Adolescent Suicide

- **Results**
  - **higher SSRI prescription rates were associated with lower suicide rates in children and adolescents**

Gibbons et al., Am J Psychiatry 163:11, 2006

SSRI Prescriptions and Observed Suicide Rate



Gibbons et al., Am J Psychiatry 163:11, 2006

What do Regulatory Agencies Say?

Medicines and Healthcare Products Regulatory Agency

- **“Only fluoxetine (Prozac) was shown in clinical trials to have a positive balance of risks and benefits for the treatment of depressive illness in under 18’s.”**

Food and Drug Administration

- Fluoxetine is the only antidepressant approved for the treatment of child and adolescent depression

What do the Experts Say?

ACNP Task Force Report on SSRIs and Suicidal Behavior in Youth

Neuropsychopharmacology (2006)

“The Task Force recommends continued use of fluoxetine as an effective and readily available treatment for major depression in youth. We believe other SSRIs need further testing to establish efficacy by use of RCTs preferably including fluoxetine as a reference compound.”

Wallace et al.

Journal of Child and Adolescent Psychopharmacology, 2006

“Fluoxetine and citalopram appear to offer favorable risk to benefit profiles, while shorter-acting agents pose greater risks and provide marginal benefit.”

Whittington et al.

Current Opinion in Psychiatry, 2005

“Current evidence supports the conclusions of the UK drug regulator in warning against the use of all the newer antidepressants except fluoxetine in this age group, and alternative therapies should be sought in the first instance. Caution is needed in interpreting drug company sponsored trials given the evidence of selective reporting and publication bias. Combining fluoxetine with a psychological treatment such as cognitive–behavioural therapy is also worth considering.”

Anything Else?

Other Considerations

- Fluoxetine is available as a generic

Summary

- **Fluoxetine has three positive RCTs supporting its efficacy. Combined, all other antidepressants have one.**
- **Fluoxetine has a more favorable risk-benefit ratio than other antidepressants.**
- **Fluoxetine is the only medication approved for the treatment of depressed children and adolescents.**

Summary

- Fluoxetine is available as a generic.
- Most experts recommend fluoxetine as the drug of choice for adolescent depression.

Medication Algorithms

- Philosophy
  - most efficacious/safest treatments first
  - simplest interventions first
  - subsequent interventions tend toward increased complexity and increased risk
  - multiple options for physicians when appropriate
  - patient preference

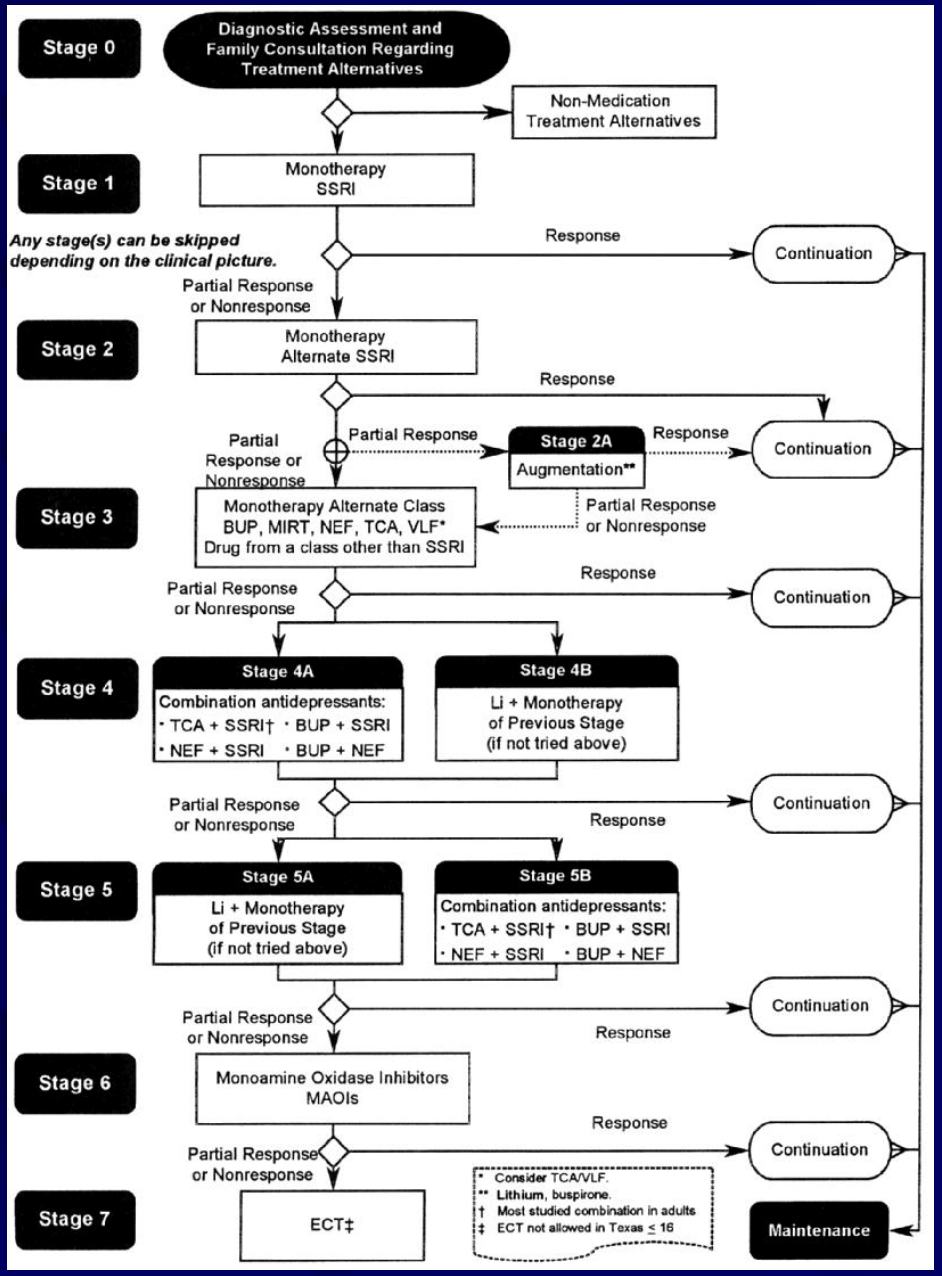
Medication Algorithms

- Clinical
  - facilitate clinical decision-making
  - improve quality of care
  - make treatment plans consistent across sites and physicians
  - provide adequate clinical documentation
  - define where new medications fit for optimal outcomes

Medication Algorithms

- **Administrative**
  - **accountability for scarce resources**
  - **uniform expectations for providers**
  - **improved cost efficiency**
  - **define where new medications are cost-effective**
  - **define costs related to specific treatments or outcomes**

Children's Medication Algorithm Project



Symptoms Severity Scales

- Clinician-rated
  - CDRS-R
  - HAM-D
- Self-rated
  - CDI
  - RADS