The Society for Clinical Child and Adolescent Psychology (SCCAP): Initiative for Dissemination of Evidence-based Treatments for Childhood and Adolescent Mental Health Problems

With additional support from Florida International University and The Children's Trust.

SOCIETY OF CLINICAL CHILD & ADOLESCENT PSYCHOLOGY

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Keynote

Evidence-based Medication Treatment for Anxiety and Depression in Young People

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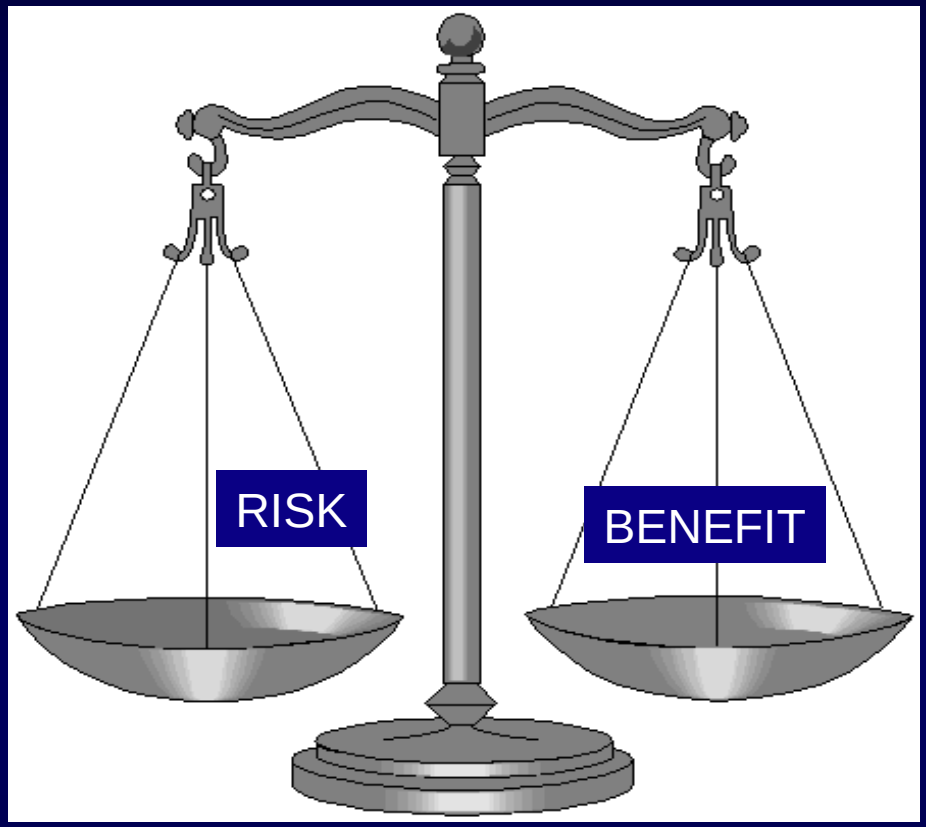
Evidence based medication treatment of depression and anxiety in young people



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Disclosure – 2011

Company	Research Support/ Honoraria/SAB
BMS	Research
GSK	Research
FIU	This presentation

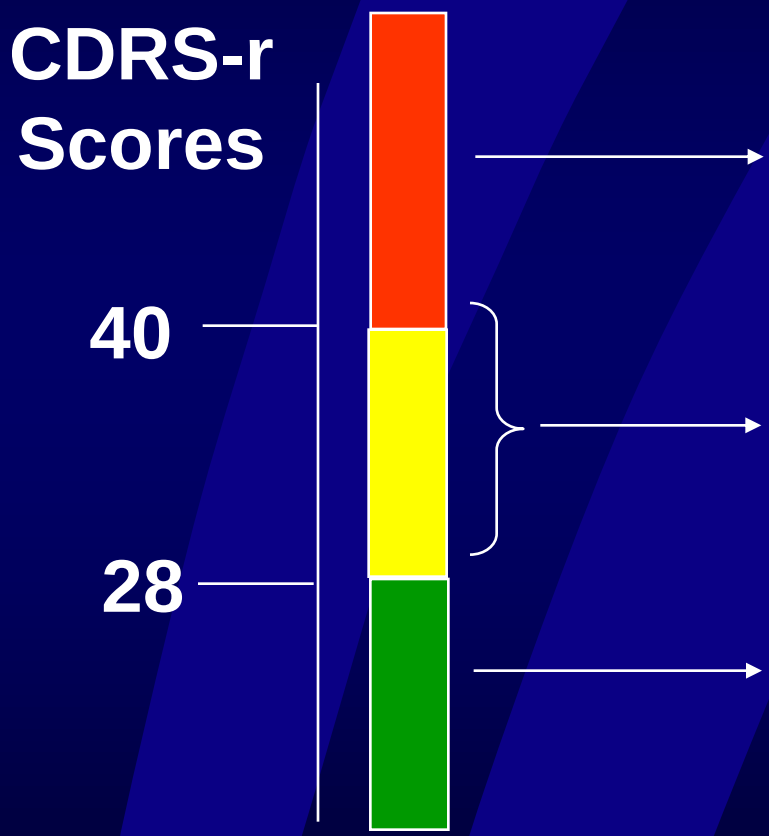
What I will cover

- How to make sense of antidepressant drug trials
- Recently published studies in the treatment of major depression (MDD)
  - (I am concentrating on MDD because findings are more controversial than for anxiety disorders but will mention those too)
- Psychiatric adverse events (aka side effects)
- How I put the information together

Ways of determining drug response

- Statistical significance: If sample size is large enough, a minor change may be statistically significant. That may have public health implications but may not have strong clinical implications for single patient.
- Effect size: Tx group minus Change in Placebo or Control group, (i.e., differential change) divided by standard deviation at baseline; http://web.uccs.edu/lbecker/Psy590/escalc3.htm
  - >0.8 =large E.S.
  - 0.5 to 0.7=medium E.S.
  - 0.2 to 0.4=small E.S.
- Absolute Treatment Benefit:
  - % drug response minus % placebo response
- Change from baseline in rating scale used
- % patients who respond/recover/no longer meet criteria for disorder

Ways of determining drug response e.g. Depression: Response vs. Remission



- **Response/Partial Response is 50% reduction in baseline CDRS score**
- **Remission:** Reduction in CDRS-r to ≤28 regardless of baseline score[1]

- lower risk of relapse[2]
- improved physical and social functioning[3]

1. Fawcett et al. *J. Clin Psychiatry*. 1997;58 (suppl 6):32-38.
2. Paykel et al. *Psychol Med*. 1995;25:1171-1180.
3. Doraiswamy et al. *Am J Geriatr Psychiatry*. 2001;9:4:423-428.

APPROVAL STATUS FOR DRUGS USED FOR INTERNALIZING DISORDERS
Positive studies are more numerous than FDA approvals for anxiety disorders

	Approved for kids	Published PBO controlled
Fluoxetine/PROZAC	MDD 8-17 OCD	MDD=4; Anx=2 OCD=2
Paroxetine/PAXIL	NO	MDD =3 SoPH=1 OCD=1
sertraline/ZOLOFT	OCD	MDD=2; OCD=2 GAD=2
Citalopram/CELEXA	NO	MDD=2
Bupriopion/WELLBUTRIN	NO	ADHD
Mirtazepine/REMERON	NO	Study done Not published
Escitalopram/LEXAPRO	MDD-12-17	MDD=1
Venlafaxine/EFFEXOR	NO	MDD=1 (2); Anx=1

Tricyclic Antidepressants (TCAs)

- Meta-analysis of the 6 studies using TCAs in children and/or adolescents (n=196):
  - None found TCA were superior to placebo
  - high placebo response rates (21% to 70% across studies) or low drug/placebo response rates
  - Stringency of response higher than in current trials
  - Effect size -0.15 in children, 0.47 in teens
- Fear of cardiovascular side effects (and the "c.y.a." of EKGs) However, comparison between PBO in and IMI in the paroxetine/IMI trial (Keller et al., 2001) also negative

Controlled Industry Pediatric Depression Trials

	Medication	Ages	Number of Studies
Positive* Studies	Fluoxetine	8-17	1 (2 NIMH sponsored)
	Sertraline Citalopram Escitalopram	6-17 7-17 12-17	2 (a priori pooled analysis)** 1
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

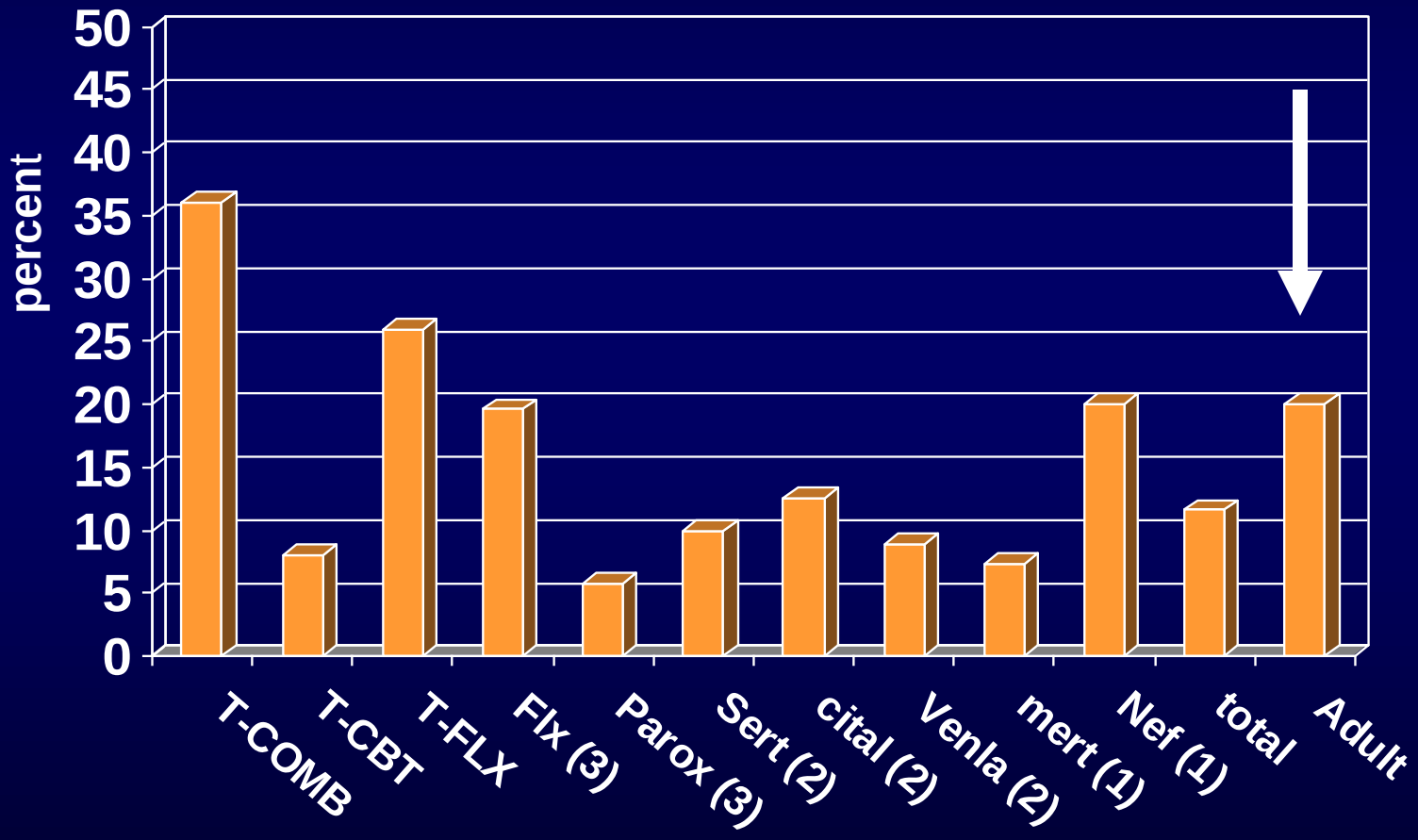
(Emslie et al, 2002; 1997; 2008; March et al, 2004; Wagner et al, 2003; 2004 Berard et al, 2006; Keller et al, 2001; Emslie et al, 2006; 2007; Wagner et al, 2006; Rynn et al, 2002; Von Knorring et al, 2006; Rynn et al, 2002; www.fda.gov/cder/foi/esum/2004/20152s032_serzone)

Absolute Benefit Increase* that can be attributed to antidepressants using various response outcomes

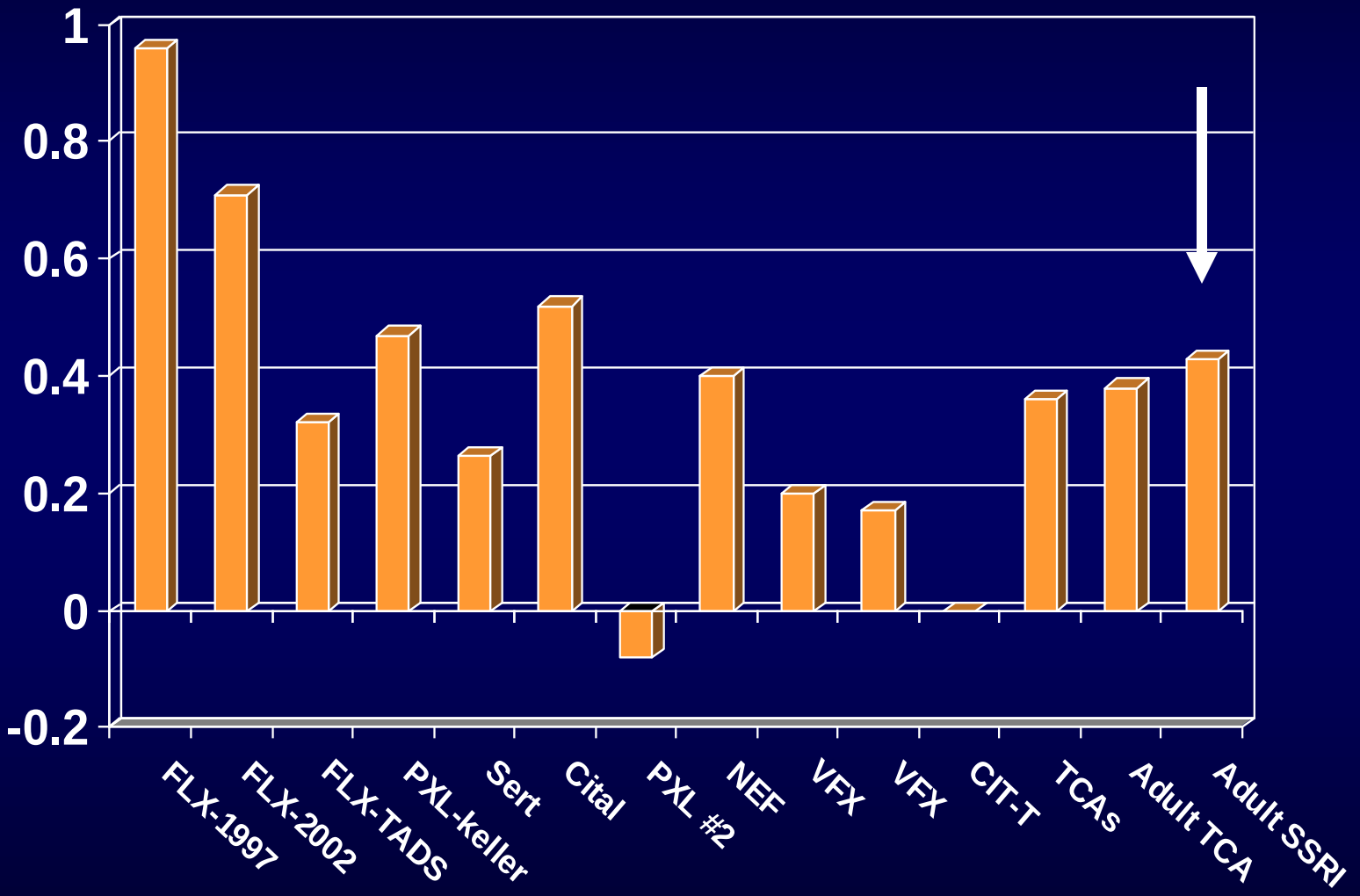
Bridge, Ann Med, 2005

(*difference between percent responded and placebo response)

number in ( ) = number of studies



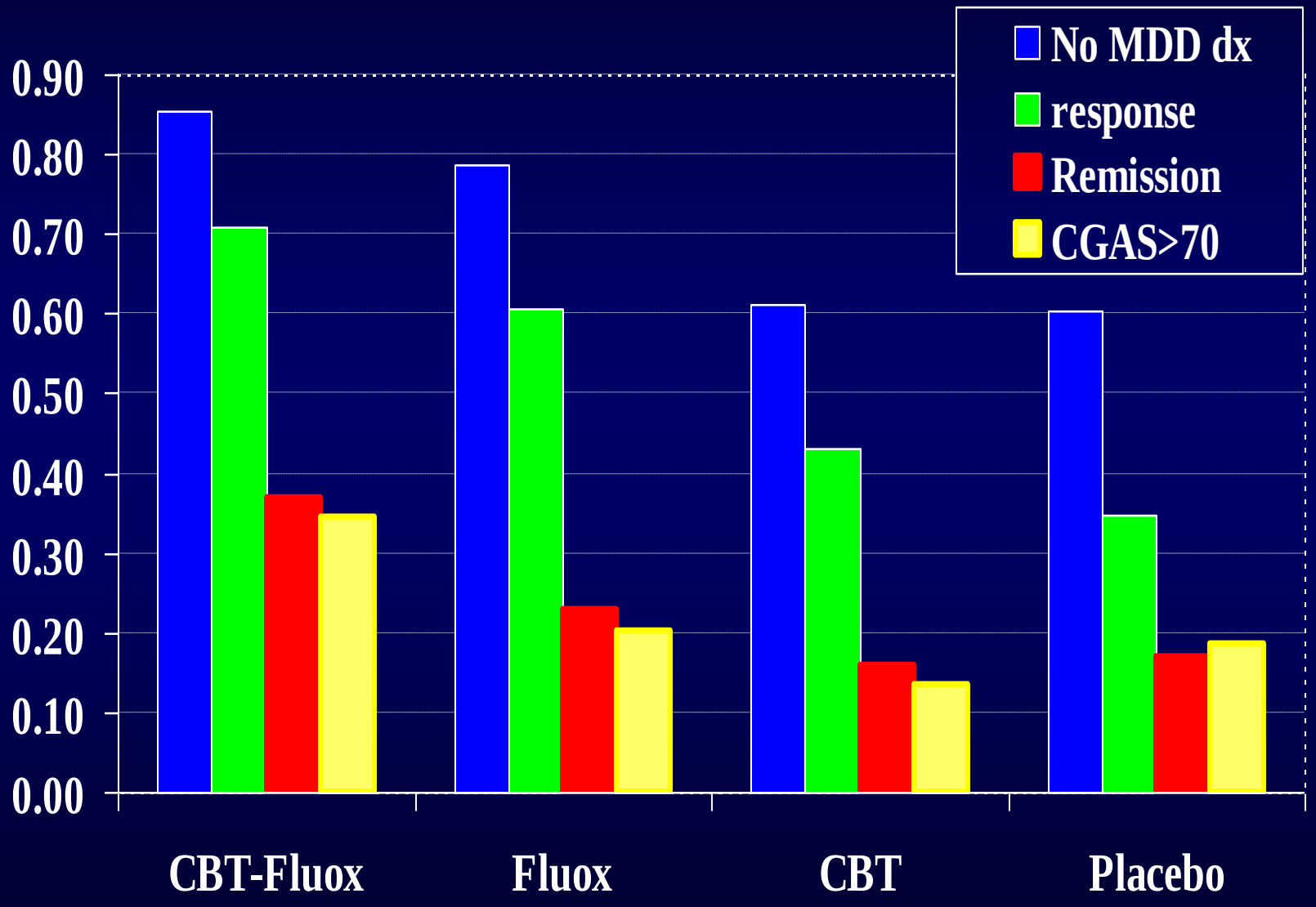
Effect sizes based on CDRS (mostly)



RECENTLY COMPLETED randomized MDD TRIALS (non-industry-14 sites)

- TADS: Treatment of Adolescent Depression Study- 12 wk with 6, 12 month f-u (any rx after 12 wks); CBT/FLX, FLX, CBT, PBO; March et al., JAMA, 2004; JAACAP
- ADAPT: Adolescent Depression Antidepressant Psychotherapy Trial-28wk, CBT/FLX, FLX; Goodyer et al., BMJ, 6/2007 (on line) [6 sites]
- TORDIA: Treatment of Resistant Depression in Adolescence; next treatment after 1st SSRI failure; Brent et al., presented at ISRCAP, June, 2007

% Remission (CDRS<28) ,response (CGI-I 1 or 2), CGAS ≥ 70 and no MDD criteria in TADS at 12 weeks



Moderators and Mediators in TADS 12 wks

Mild to moderate depression: COMB>FLUOX>CBT=PBO

Moderate to severe depression:COMB=FLUOX>CBT=PBO

Poor response = Indicators of ↑ depression severity:

- Higher scores in depression scales
- Long duration
- Suicidal ideation/attempts
- ↑Hopelessness
- Poor functioning

Poor response (psychological predictors)

↓ expectations to treatment benefits

↓ Coping skills

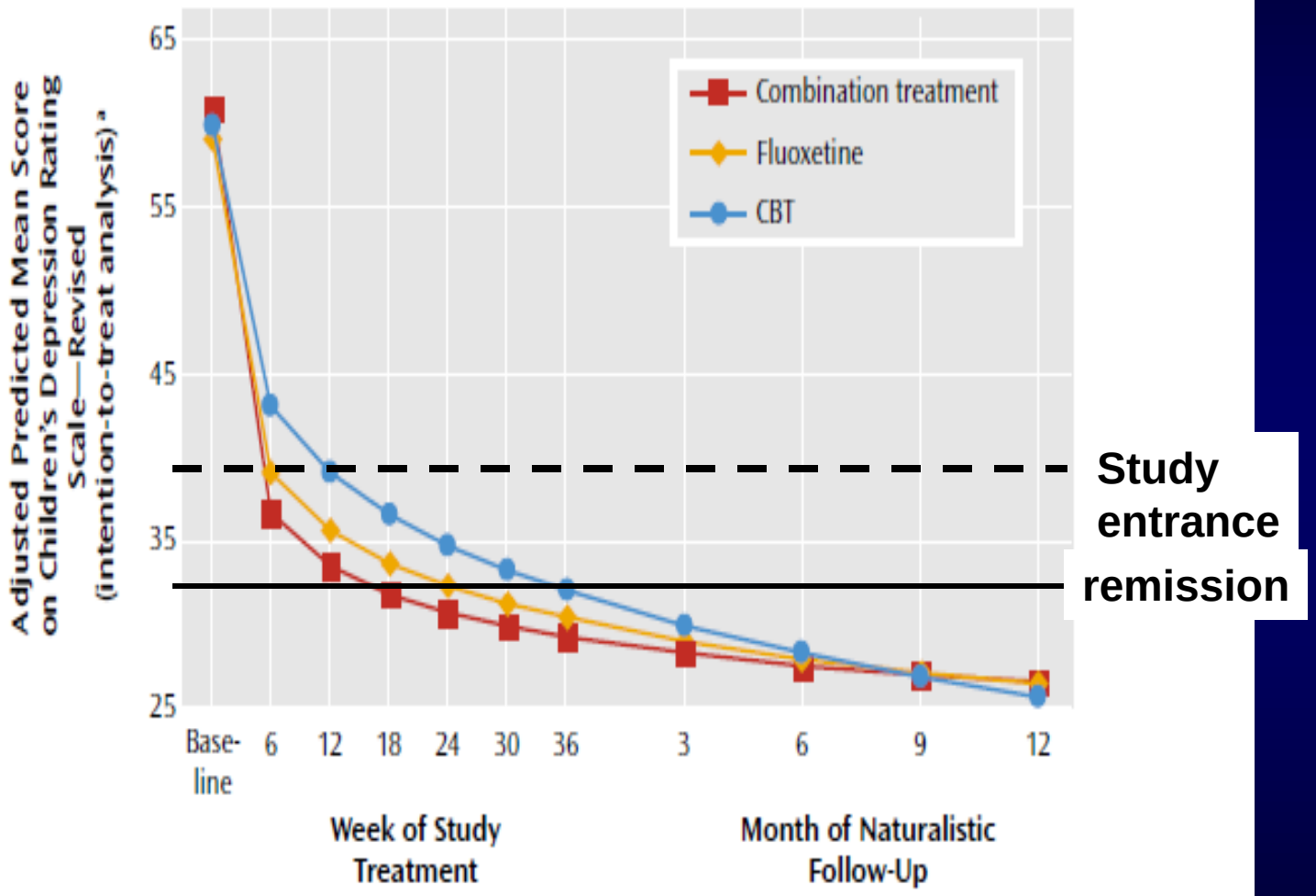
↓ Socio-economic Status

↑ Comorbid disorders

↑ Family conflict and dysfunction

↑ Exposure to negative events (e.g., abuse)

FIGURE 1. Depression Scores From Baseline to End of Naturalistic Follow-Up for 327 Adolescents With Major Depres
Disorder Treated With Fluoxetine, Cognitive-Behavioral Therapy (CBT), or a Combination

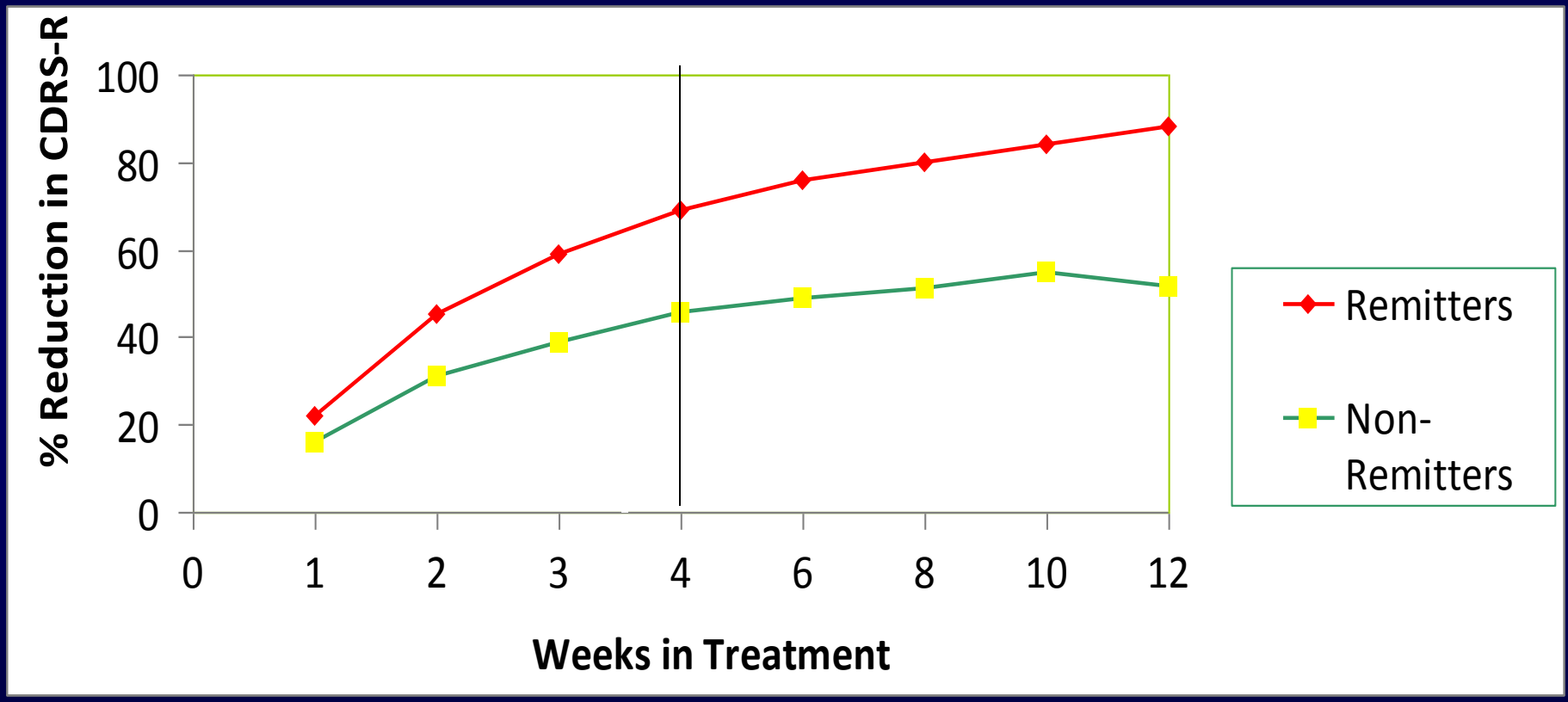


[a] Derived from the random coefficients regression model with adjustments for fixed and random effects.

TADS Team, Am J Psychiatry 2009; 166:1141-1149

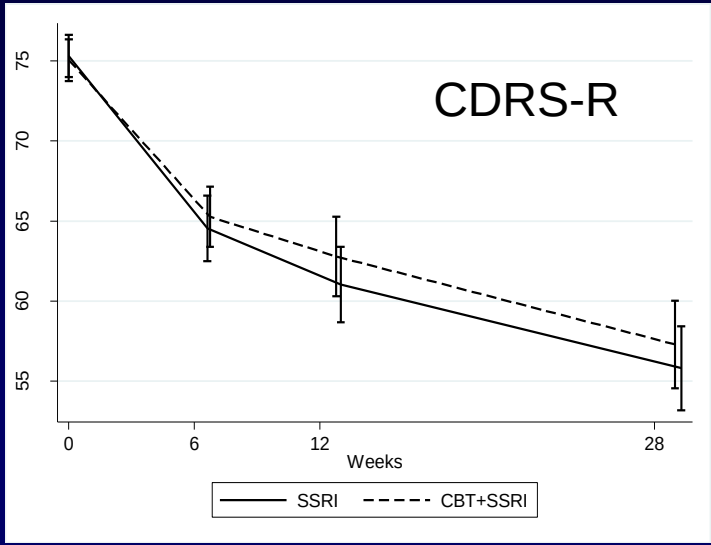
At what point can you determine that response/remission is likely?

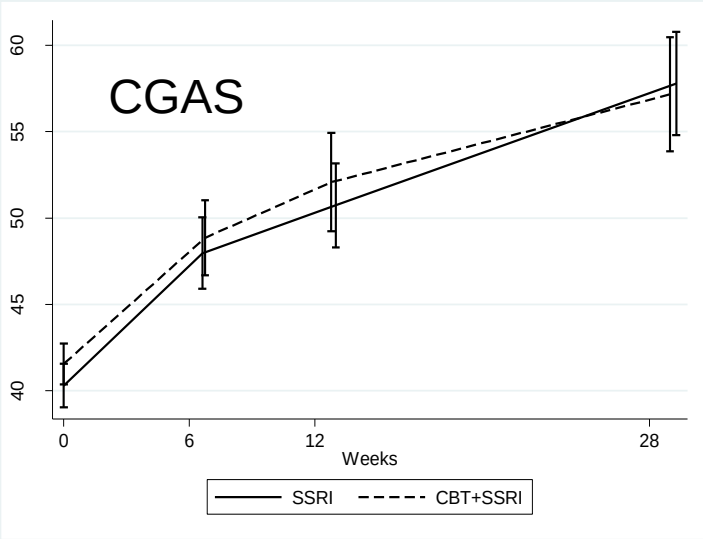
N=168- Open label Fluoxetine

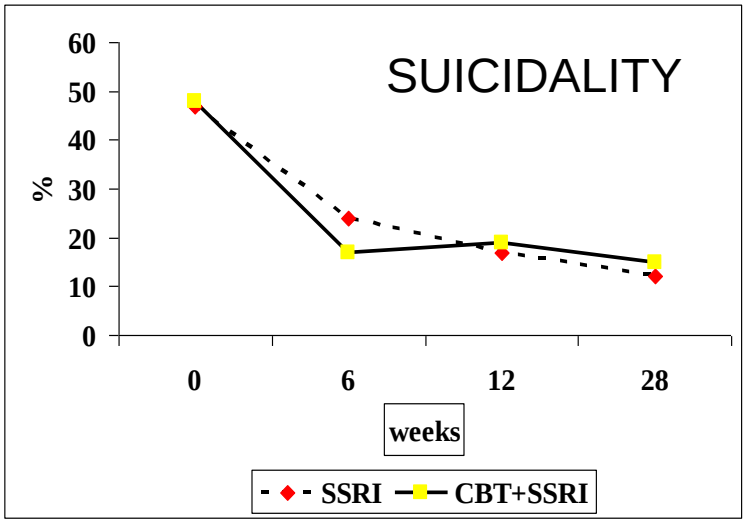


At week 4, a CDRS-R reduction of ~50% best discriminates remitters from non-remitters; as effective with children as teens; + Fam hx a predictor; (Tao et al, J Am Acad Child Adolesc Psychiatry, 2009; 48:71-78)

Outcomes in ADAPT – A UK study of Flx and CBT; no placebo







% CGI very much or improved but CDRS-R never ≤28

	SSRI	CBT + SSRI
6 weeks	35.8%	35.0%
12 weeks	43.6%	41.6%
28 weeks	60.7%	53.1%

Goodyer et al., Br. J. Psychiatry, 2008

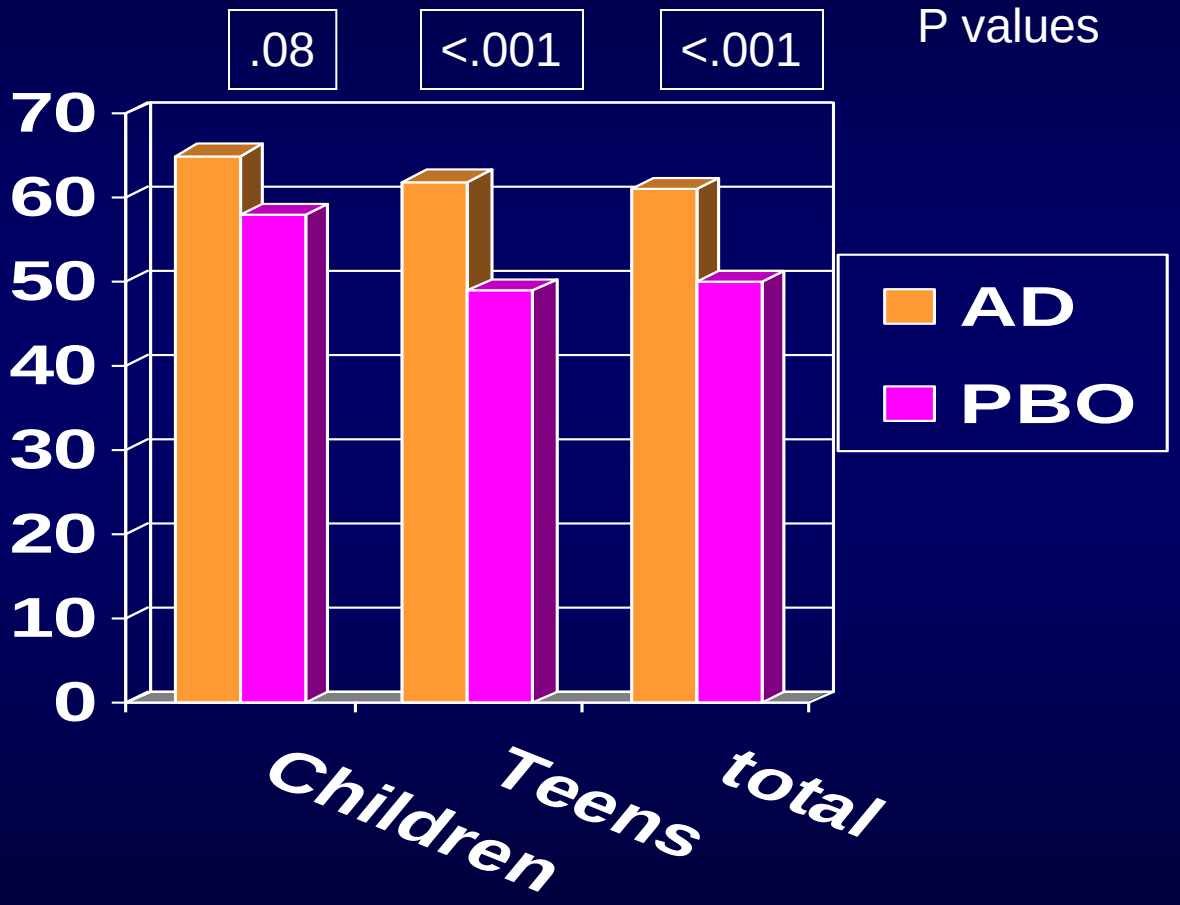
COMPARISON OF ADAPT AND TADS TRIALS

	ADAPT N=208 r 6 sites Age 11-17	TADS N=439 r 13 sites 12-17
% comorbid	89	52
X HoNOSCA Health and Sociial Funing Scale	25	17
X CDRS	59	60
X CGAS	41	50
% suicidal	47%	27%
	SSRI-CBT	SSRI-CBT
3, ~ 6mo resp	41% 53%	71% 80%
3, ~6mo Honosca	17 15	10.6 (7.9)
12 mo CDRS	Dropped 1.5 sds	Dropped 2 sds

Age related Antidepressant response in MDD

Bridge et al., JAMA 297:1683, 2007

Safer, Pediatrics, 2007



Reasons for modest response rate

- High placebo response rates; rates children > teens> adults (Bridge et al., JAMA 297:1683, 2007 ; Safer, Pediatrics, 2006, 118(3):1248-51)
- Increasing placebo response with year of study (Walsh, 2003)
- Pharmacokinetics differ a little in young people (Findling et al.,JCAP 2006)
- In MDD trials, decrease in the magnitude of antidepressant treatment effects as the number of study sites increased. (Bridge et al., 2007)
- In 9 of 15 MDD trials less efficacy with longer duration of illness. (Bridge et al., 2007)
- Some think that higher rate of child BP decreases response rate but lithium treatment in putatively bipolar depressed children had no effect (Geller et al.,)
- Duration of trials aren't long enough (ADAPT Study) **though recent data indicate most response is evident by 4-6 weeks** (Tao et al., 2009)
- Drugs just aren't effective enough (Carlson, now)

Predictors of placebo response in internalizing disorders

Cohen et al., JCAP 20:39-47, 2010

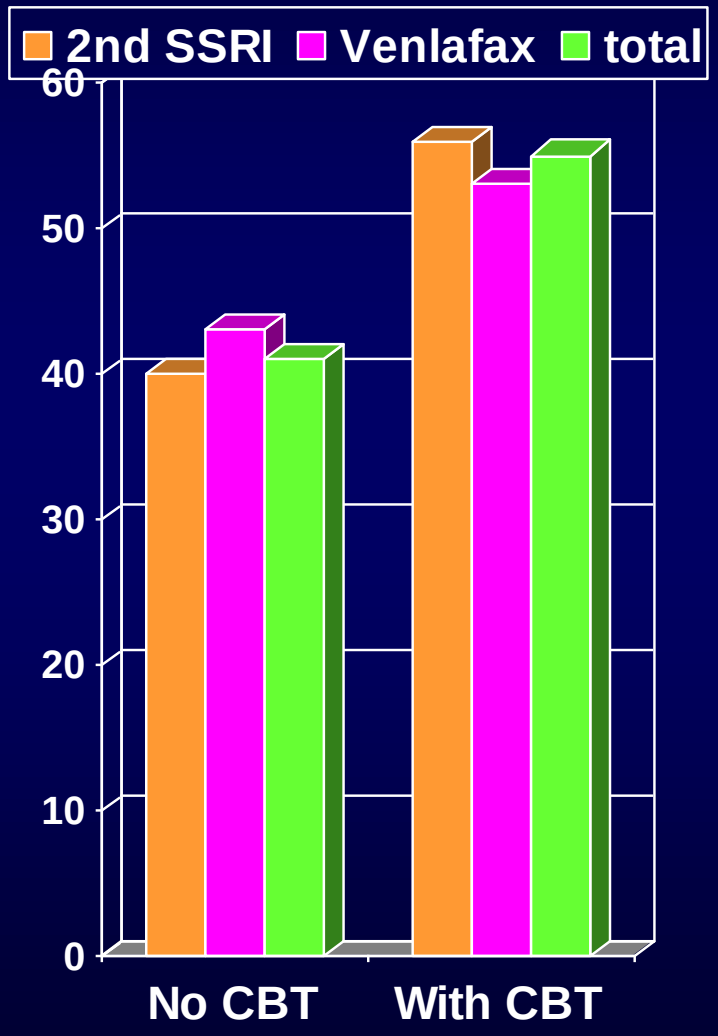
- Lower placebo response rate associated with
  - Caucasian race
  - Male gender
  - Washout period in the study
  - Longer illness duration
  - Type of internalizing disorder: OCD 31% (range 4-41%) < Anxiety disorder 39.6% (9-53%) < MDD 49.6% (17-90%)
  - RULE OF THUMB: When placebo response <33%, drug superior; when >40%, placebo superior

TORDIA (Brent et al., JAMA 2008; 299:901–913)

next treatment after 1st SSRI failure

- 7 years to complete
- 334 teens –no or incomplete response to adequate trial of 1 SSRI (investigators continued this 2 more wks, raised dose 2 weeks before starting-only 6% of original sample responded)
- Randomized to another SSRI (paroxetine, citalopram, sertraline), SNRI (venlafaxine), or CBT added to either 2nd antidepressant or venlafaxine

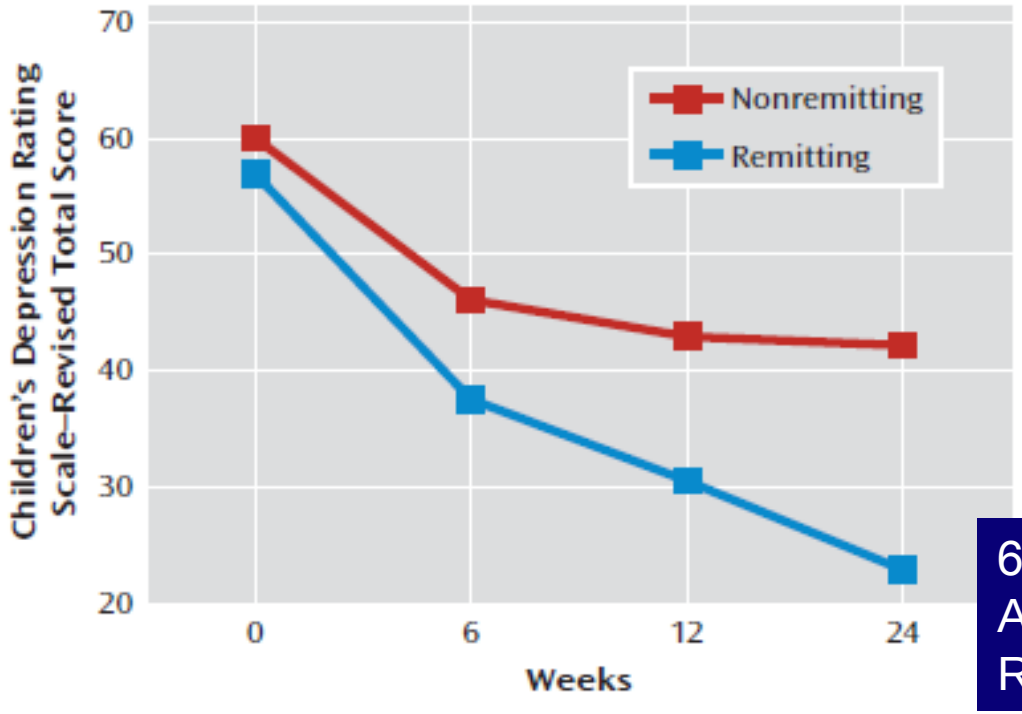
- Blinded treatment for 12 weeks, then open treatment for 12 wks then naturalistic follow up
- 6 sites



TORDIA data at 24 months

Emslie et al., Am J Psychiatry, 2010

FIGURE 3. Reduction in Children's Depression Rating Scale–Revised Scores Among Subjects in the Treatment of Resistant Depression in Adolescents (TORDIA) Study[a]



[a] Log time: p<0.001; remission: p=0.07; remission-by-log time: p<0.001.

Type of AD or CBT
Did not impact time
To remission or
Time to relapse

61.6% of whose who'd remitted
At 24 months had shown a clinical
Response by wk 12 (vs 18.3%).

Response – CGI ≤2or 50% drop on CDRS; Remission- 3 wks of ≤1 dep symptom; Relapse-2wks of definite or probable depression

TORDIA-Naturalistic follow up

Vitiello et al., J Clin Psychiatry, 2010

Cumulative REMISSION rate

12 wks-17.7%

24 wks – 38.9%

48 wks - 50%

72 wks-61.1%

Median time to remission-25 wks

~30% of remitters still had low self esteem, irritability, fatigue

Remission predictors:

- Lower depression scores (CDRS, BDI etc)
- Shorter episode
- Lower CGI-severity
- Higher CGAS
- Less NSSI
- Less SUD

Demographic variables and comorbidity were not predictors

TORDIA-Naturalistic follow up

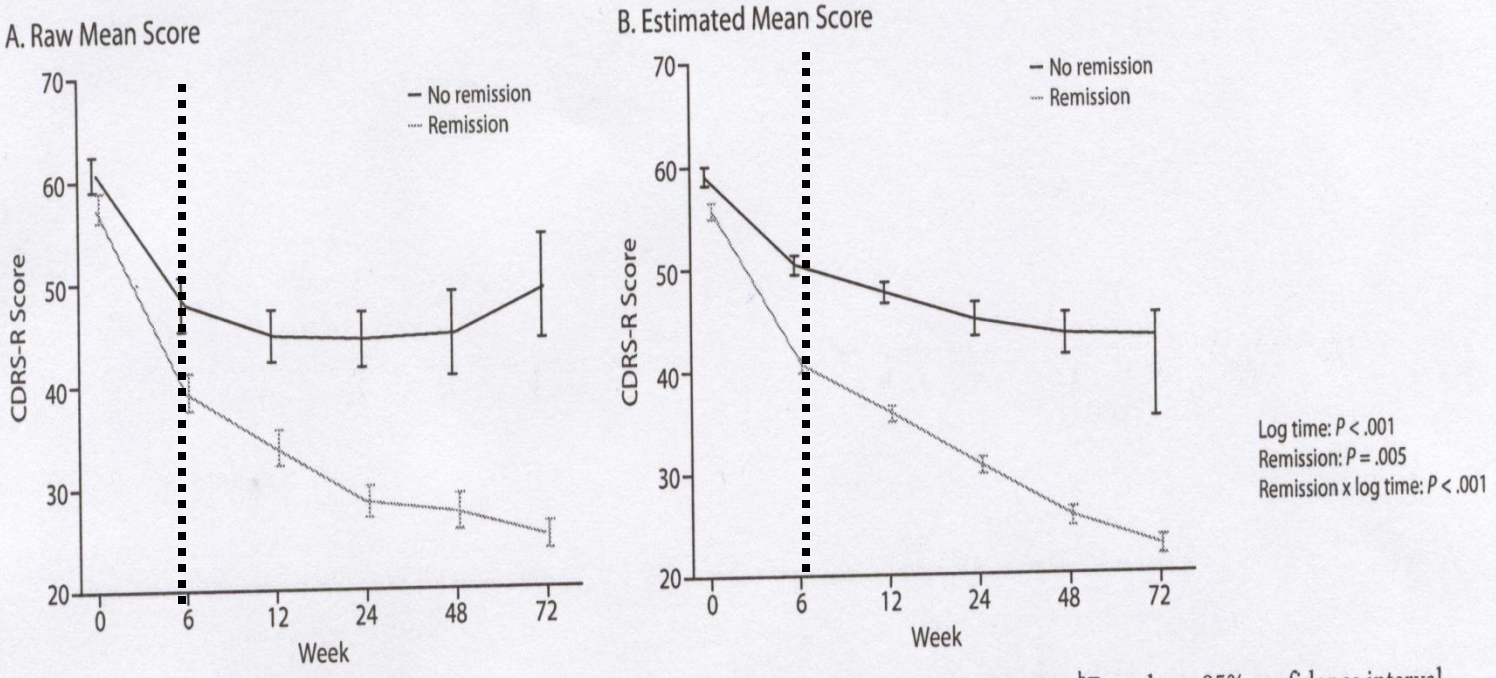
Vitiello et al., J Clin Psychiatry, 2010

- Relapse between 24 and 72 weeks was 25.4%
- Type of treatment (med only, CBT, SSRI or venlafaxine) didn't matter
- Correlation between CDRS-R and CGAS was r= -.66
- Suicidality declined but those on venlafaxine showed less decline ($p<0.03$)

Long term outcome of TORDIA sample

Vittiello et al., J. Clinical Psychiatry, 2010

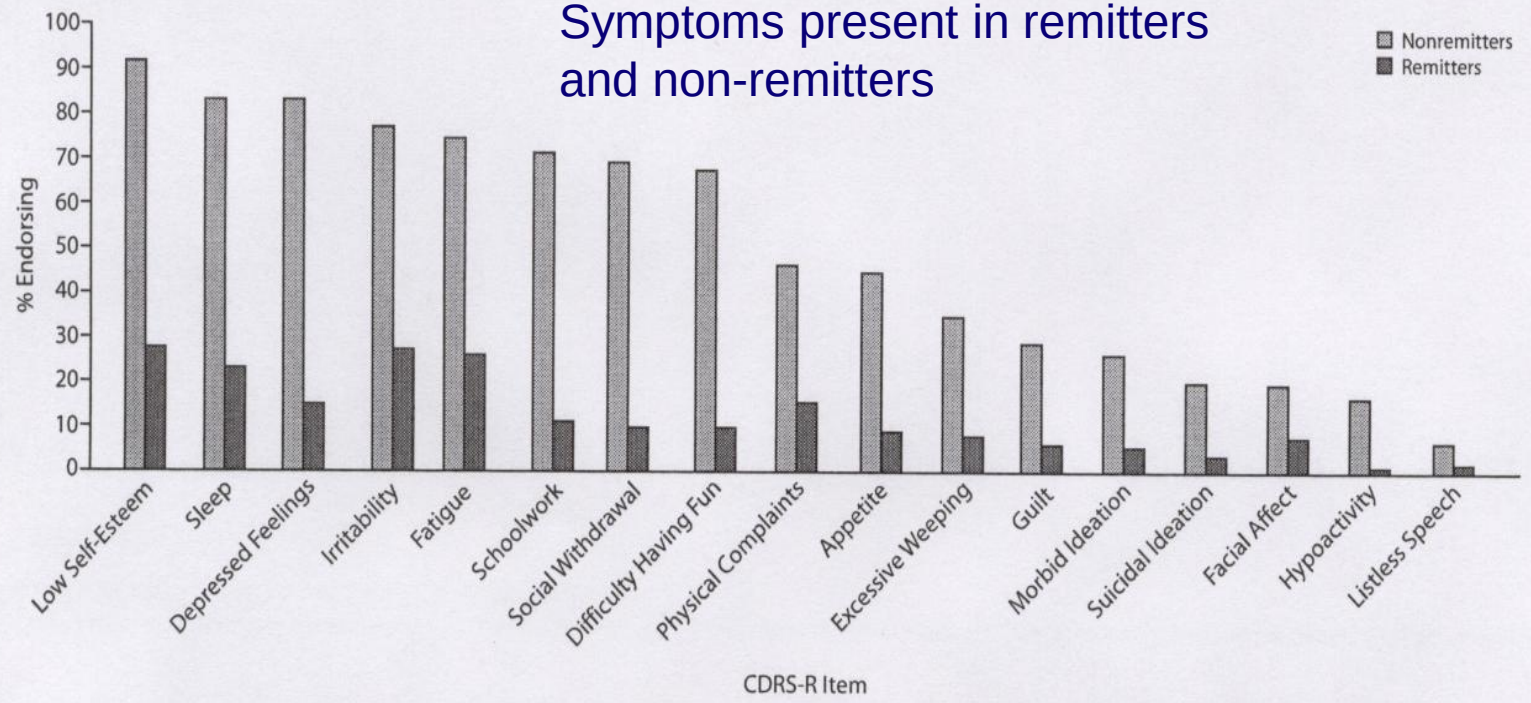
Figure 3. Trajectories of Depression Symptoms (Children's Depression Rating Scale–Revised Version [CDRS-R]) by Remission Status at Week 72[a,b]



[a]At week 6, remitters had lower CDRS-R scores (39.5 ± 12.7 than nonremitters (49.9 ± 3.6), $t_{331} = 7.15$, $P < .001$. [b]Error bars: 95% confidence interval.

Long term outcome of TORDIA sample

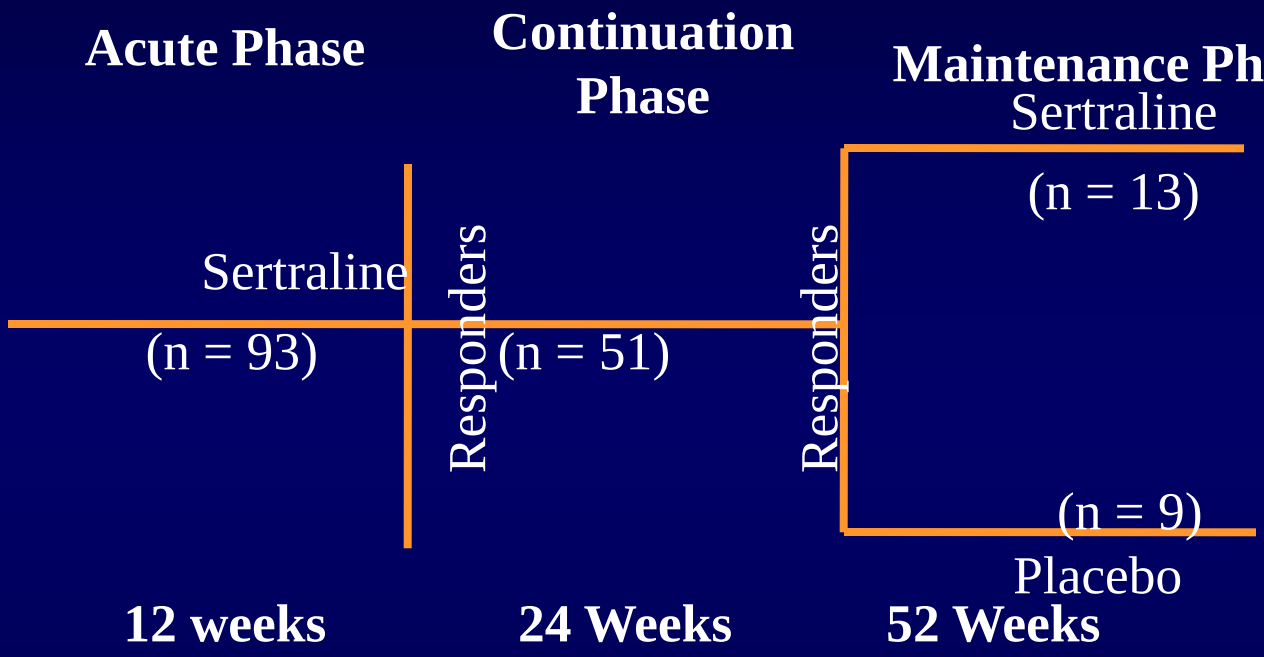
Vittiello et al., J. Clinical Psychiatry, 2010



[a]Percentage of participants assessed at 72 weeks (n = 173) endorsing (score of 3 or above) specific symptoms of the CDRS-R. [b]Percentage of participants assessed at 72 weeks who had reached remission (n = 138) or not (n = 35) in TORDIA, endorsing (score of 3 or above) specific symptoms of the CDRS-R. Remission is defined as at least 3 consecutive weeks without clinically significant depressive symptoms, corresponding to a score of 1 on the A-LIFE.

Abbreviations: A-LIFE = adolescent version of the Longitudinal Interval Follow-Up Evaluation, CDRS-R = Children's Depression Rating Scale–Revised Version, TORDIA = Treatment of Selective Serotonin Reuptake Inhibitor (SSRI)–Resistant Depression in Adolescents study.

Maintenance Treatment for Adolescent Depression



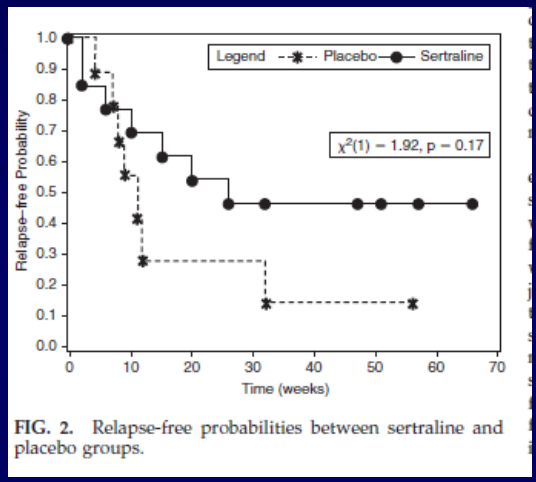


FIG. 2. Relapse-free probabilities between sertraline and placebo groups.

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

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

Summary of treatment studies of adolescent depression-CBT

Walkup editorial, Am J Psychiatry, 2010

- CBT and medication > medication alone on some outcomes (e.g. suicidality) in TADS but not ADAPT or TORDIA
- CBT doesn't add much in severe depression.
- In the TORDIA acute phase, the groups getting combined treatment had an approximately 10% greater response rate, but this between-group difference did not persist to week 24.
- TORDIA, like ADAPT, did not find a signal for for the protective effects of CBT.
- Depression is different from anxiety in this regard, as well as in response to SSRIs

Summary of treatment studies of adolescent depression-Meds

Walkup editorial, Am J Psychiatry, 2010

- Clinic visits were weekly and dose adjustments brisk.
- Data suggest that doses should be adjusted quickly and to use adequate doses
- For complex or treatment resistant cases, find that out soon.
- How long to wait before switching antidepressants is not fully established, but remitters usually demonstrate improvement by 8–10 weeks.
- Minimal response or failure to respond by 8–10 weeks does not preclude later improvement, but clinicians should be prepared for the management of resistant depression early in treatment.

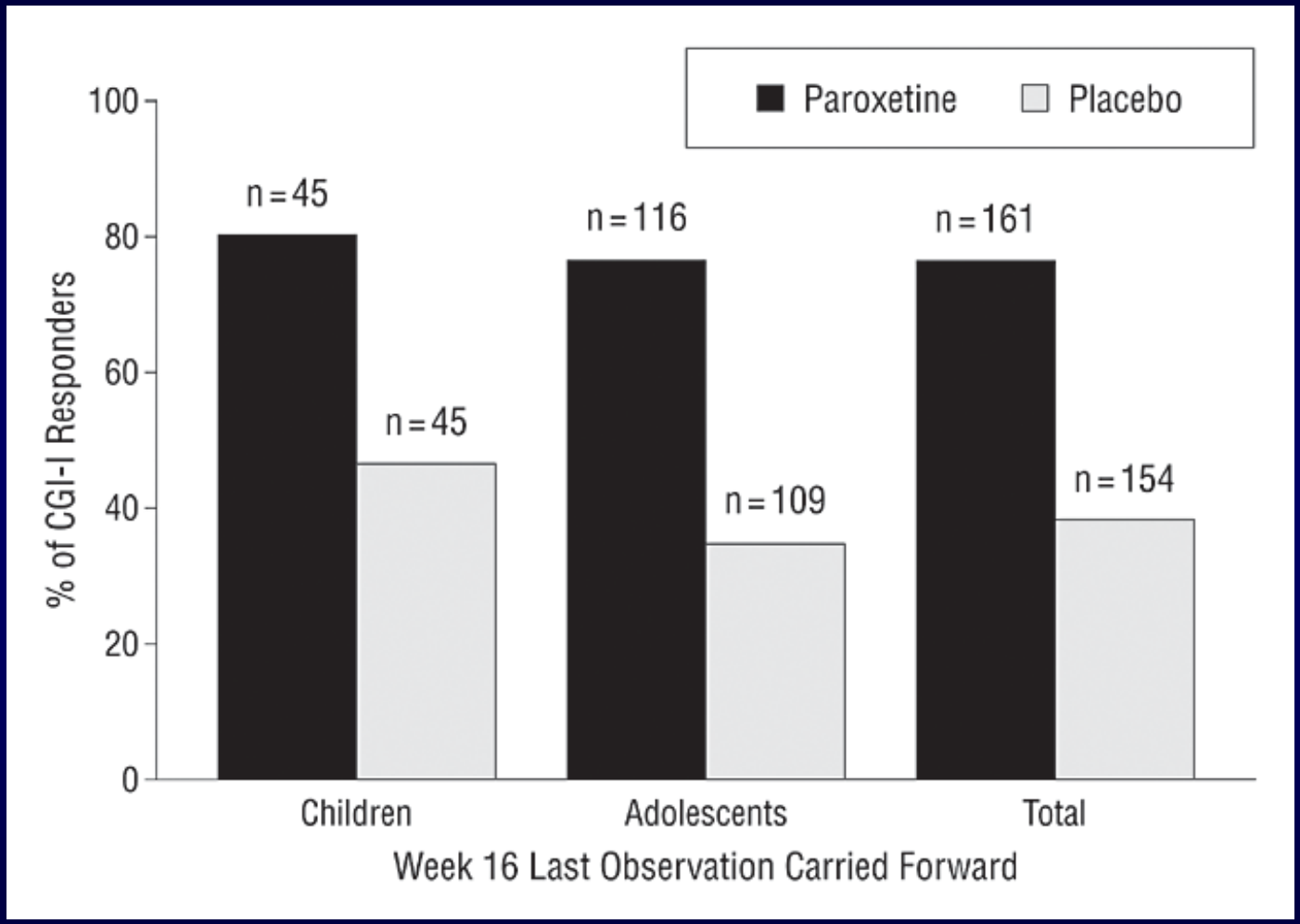
Treatment of TEEN (vs child) depression

- Investigator-initiated studies such as TADS, APADT, and TORDIA (as opposed to industry-sponsored studies which have high placebo response rates) suggest that treatment for teen depression that includes medication is effective and can be implemented safely.
- It is important to make sure that teens get to the clinic and get there early in their course of illness.

Bottom line benefit for MDD in children and adolescents

- Drug produces some improvement in 61% of children and adolescents; placebo works in half (50%) of the participants Bridge et al., JAMA 297:1683, 2007
- The teen response is more robust than the child response Bridge et al., JAMA 297:1683, 2007
- Teen response > child response because placebo response lower Bridge et al., JAMA 297:1683, 2007
- In general, efficacy was inversely proportional to duration and severity of depression Bridge et al., JAMA 297:1683, 2007; Goodyer et al., BMJ 2007
- CBT OK in mild depression; may add to treatment resistant depression (TORDIA)
- Close follow up with attentive treatment is needed
- Algorithm: SSRI→SSRI+CBT→ 2nd SSRI/SNRI + CBT

Proportion (CGI-I) responders (intention-to-treat population) for children and adolescent subgroups and total -week 16 LOCF for ANXIETY disorders

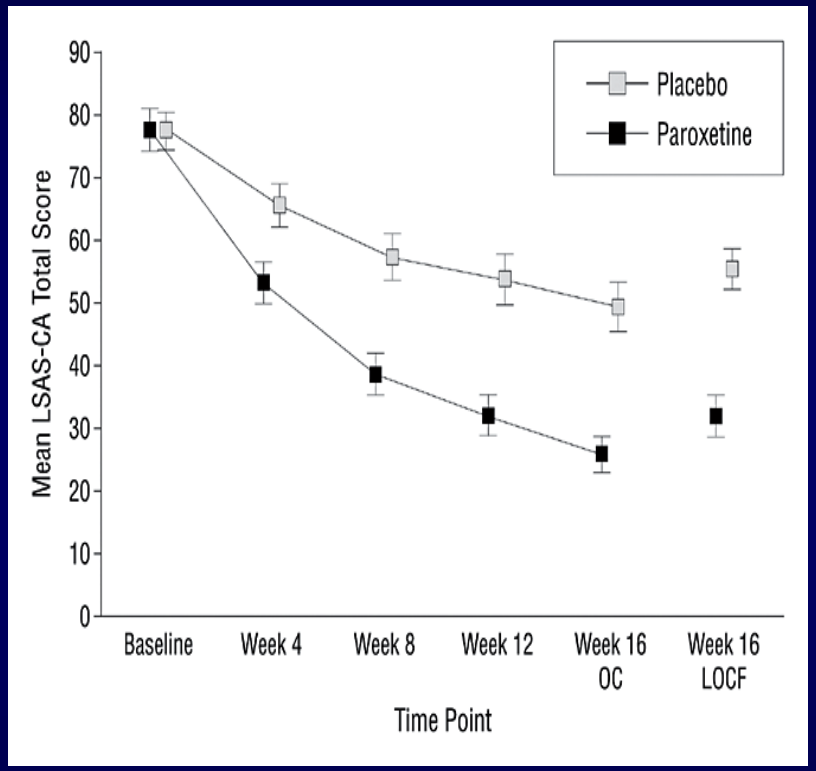


Wagner, K. D. et al. Arch Gen Psychiatry 2004;61:1153-1162.

ARCHIVES OF GENERAL PSYCHIATRY

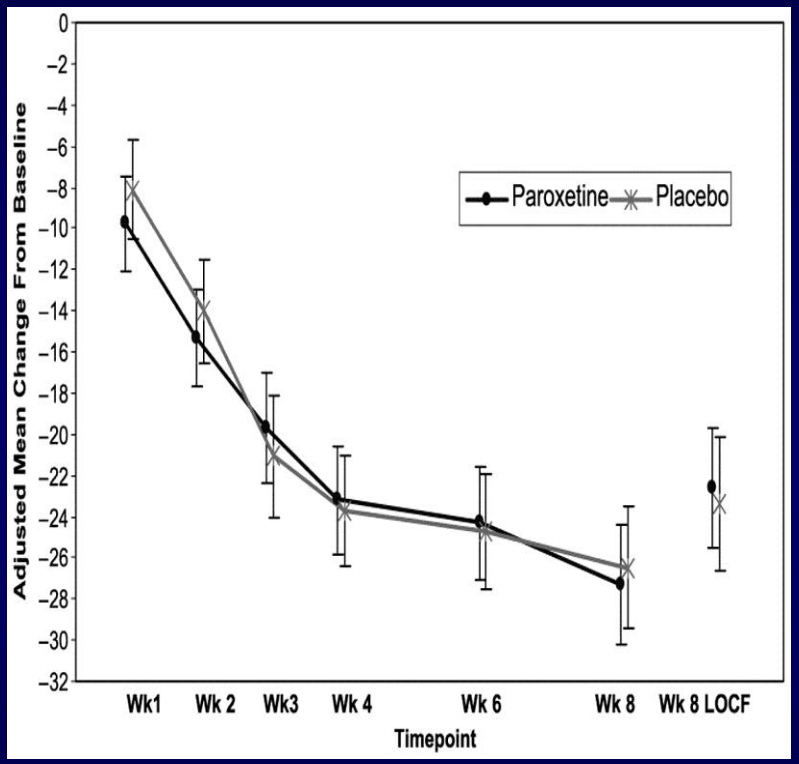
Same drug and dose; different conditions

SOCIAL PHOBIA



Wagner, K. D. et al. Arch Gen Psychiatry 2004;61:1153-1162.

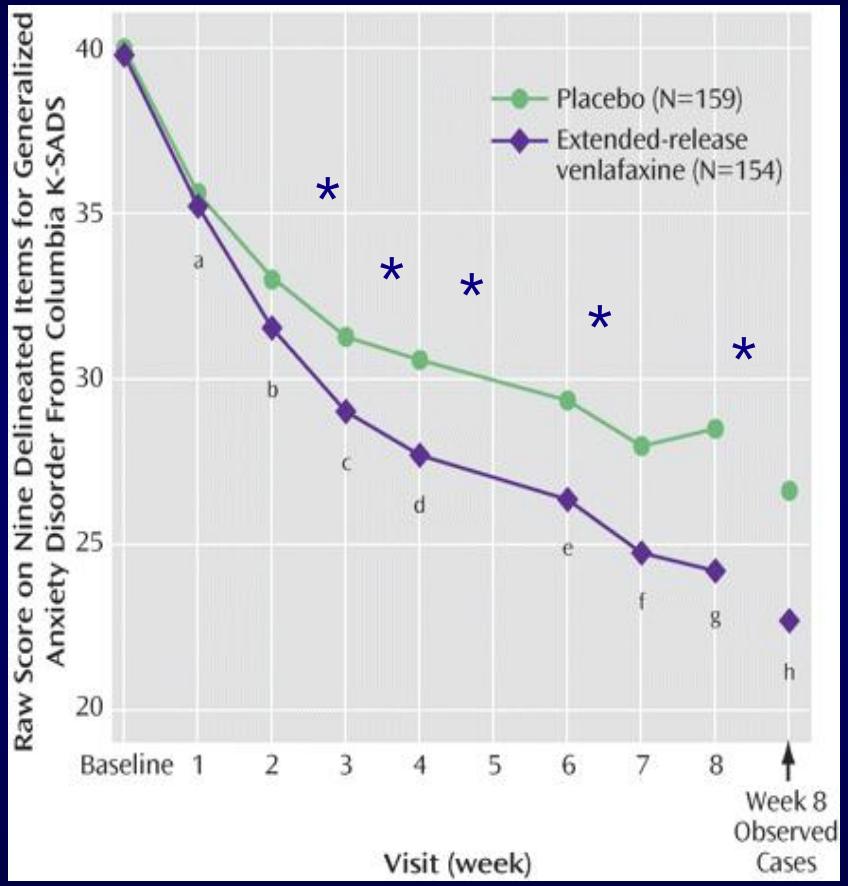
MAJOR DEPRESSION



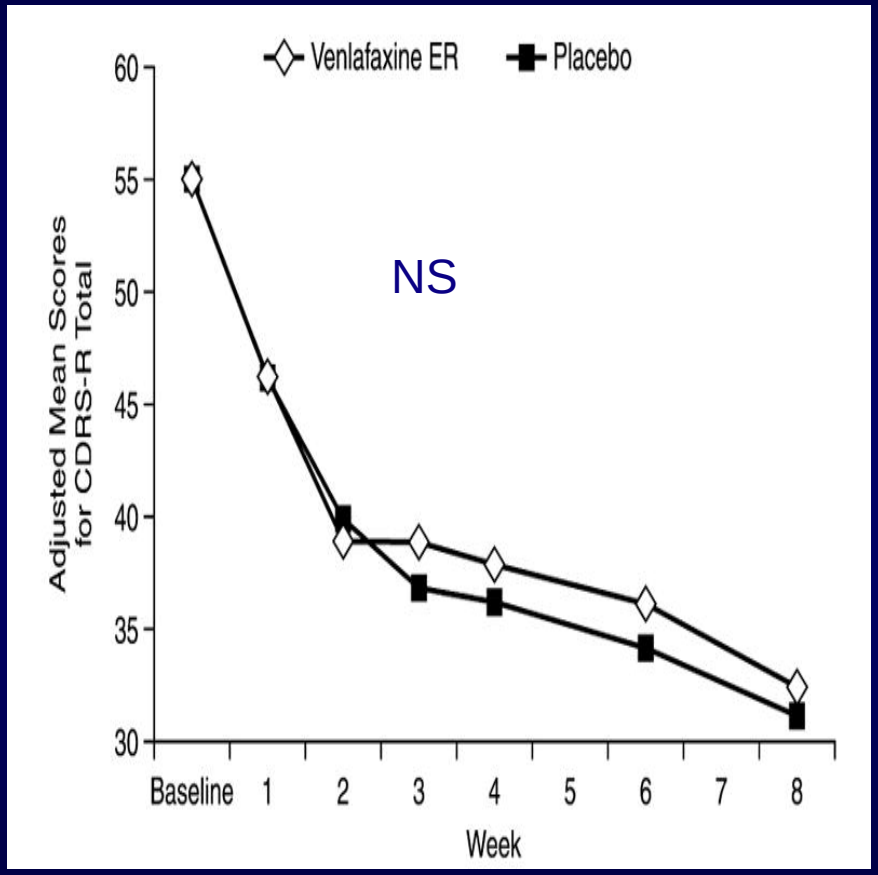
Emslie et al; JAACAP, 45:709, 2006

Same drug and dose; different conditions

GENERALIZED ANXIETY DISORDER



MAJOR DEPRESSION

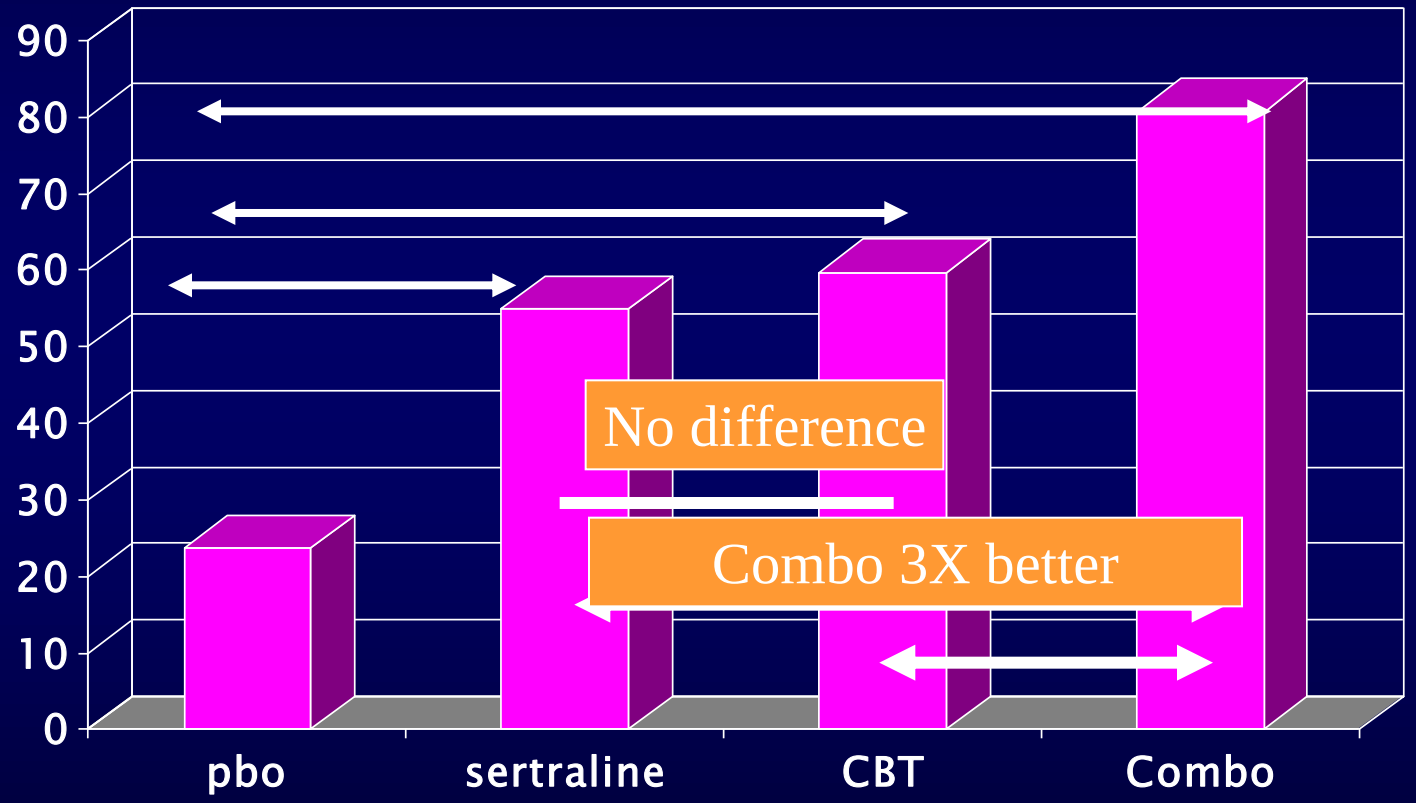


Venlafaxine ER in GAD
Rynn et al Am J Psychiatry 164:290-300 , 2007

Venlafaxine ER in MDD ; Emslie et al., JAACAP 46: 479-488 , 2007

Efficacy of CBT, SSRI and both in anxiety disorders in youth

Walkup et al., NEJM, 2008



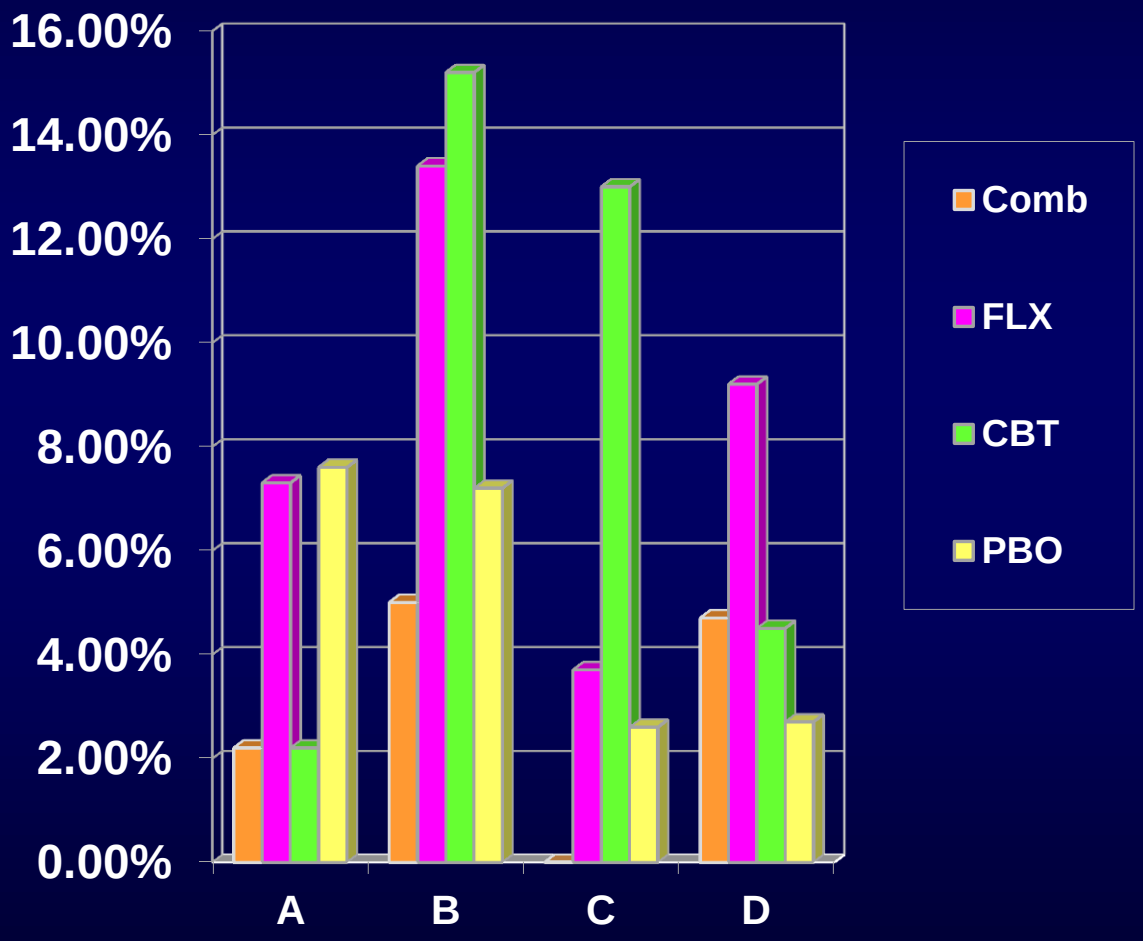
Issues with adverse events

- How elicited?
  - Spontaneous or by rating scale
  - How thorough is the rating scale
  - Do rating/sponatneous reports agree with each other
- Determined a priori like efficacy?
- If present, how serious?
  - Did it cause study drop out
  - Was the symptom present but not troubling
  - Can you tell if it is a symptom of the condition or the treatment

Suicidality in TADS-note different measures

Emslie et al., JAACAP, 2007

- A=> 31 on Suicidal Ideation Questionnaire
- B=Suicidality item on the CDRS-1 point
- C=5 point CDRS increase
- D=Any spontaneous report/Vetted through the Columbia rating



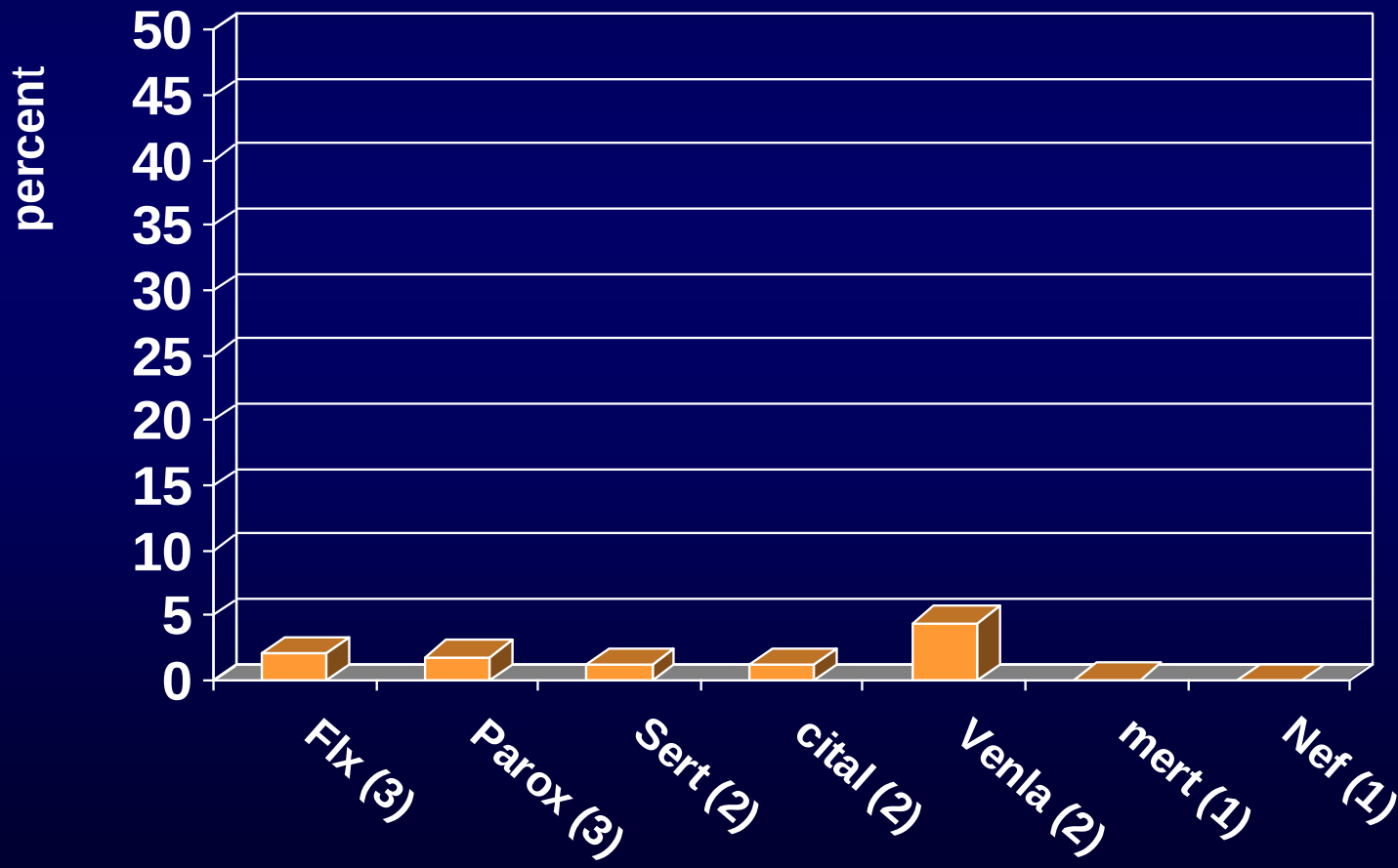
CDRS-r Suicidal ideation item

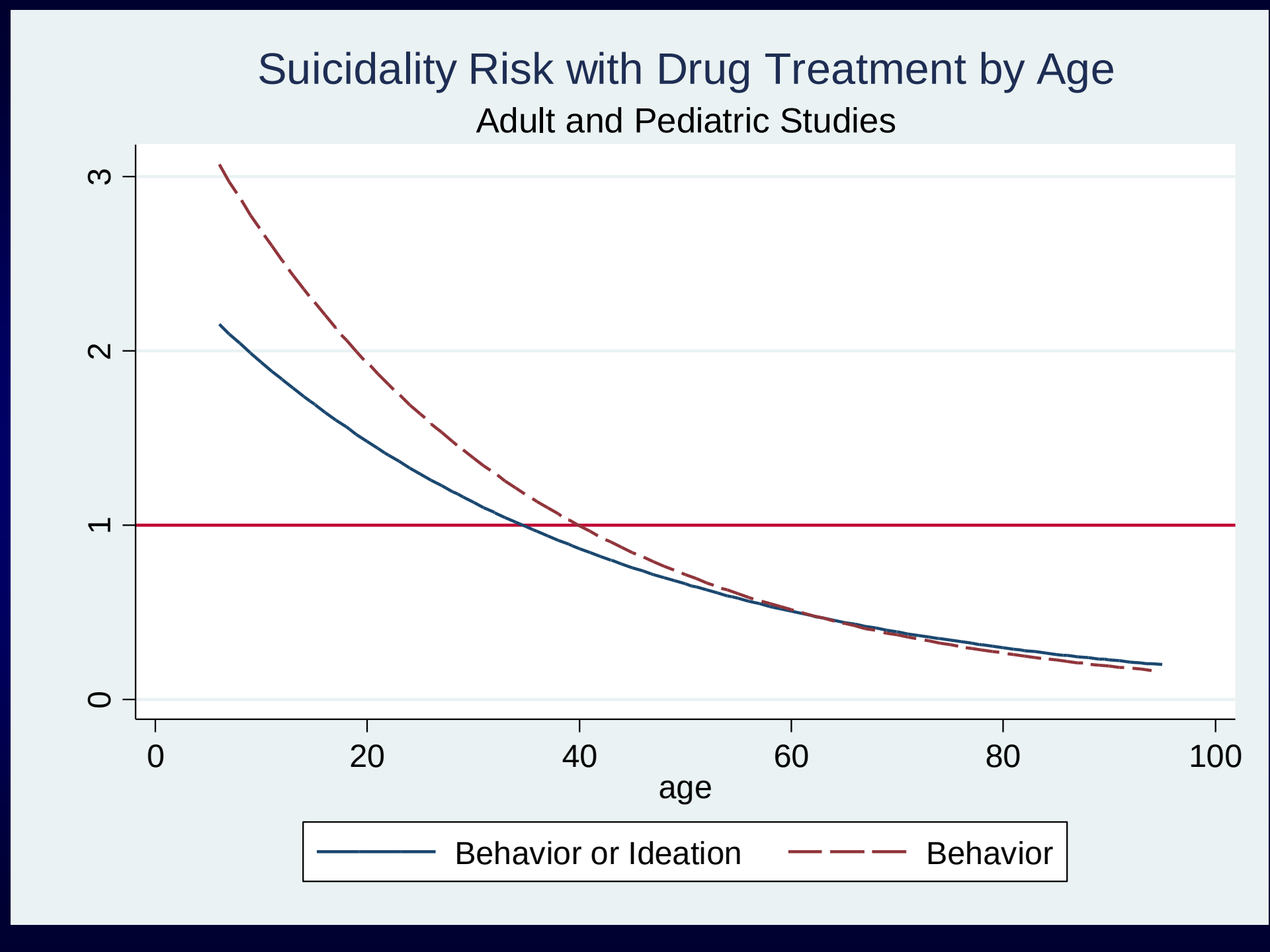
13. **SUICIDAL IDEATION**

- ☐ 1 Understands the word "suicide" but does not apply the term to himself/herself
- ☐ 2 Sharp denial of suicidal thoughts
- ☐ 3 Has thoughts about suicide, or hurting himself/herself (if he/she does not understand the concept of suicide), usually when angry
- ☐ 4
- ☐ 5 Has recurrent thoughts of suicide
- ☐ 6
- ☐ 7 Has made a suicide attempt within the last month or is actively suicidal

Absolute Suicidal Behavior Increase* that can be attributed to intervention using various response outcomes Bridges, Ann Med, 2005

(*difference between percent drug and placebo response)
number in ( ) = number of studies



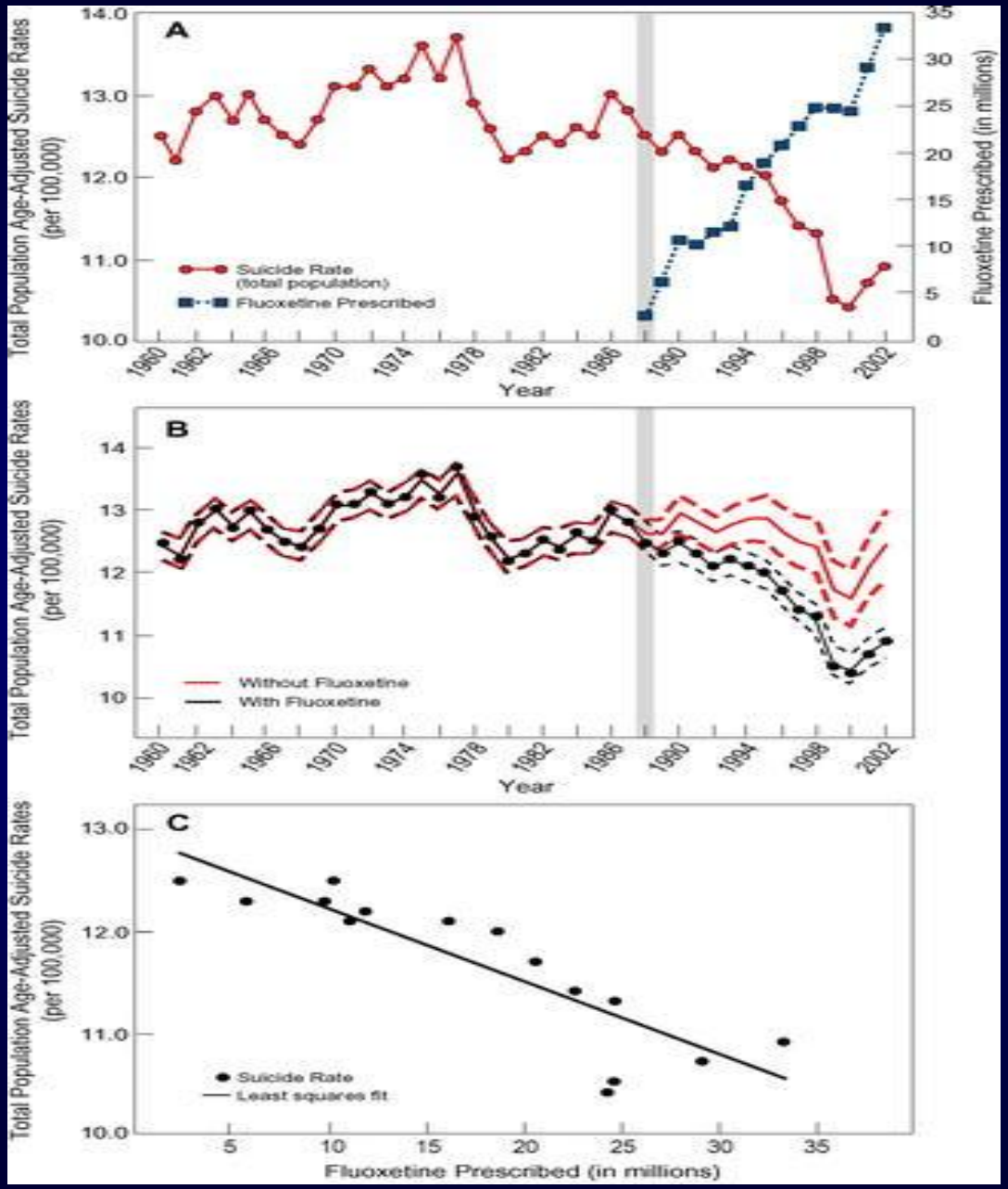

Suicidality Risk with Drug Treatment by Age
Adult and Pediatric Studies
3
2
1
0
0
20
40
60
80
100
age
Behavior or Ideation
Behavior

Suicidal Ideation/Suicide Attempts in Placebo-Treated Participants

(Bridge et al., JAMA, 2007)

- Among participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials (odds ratio, 9.9; 95% CI, 1.6 to 406.3) and OCD trials (odds ratio, 5.8; 95% CI, 0.9 to 237.3)
- these effects were limited to adolescent participants. There was no evidence of a treatment x indication x suicidal ideation/suicide attempt interaction (*P* = .53).

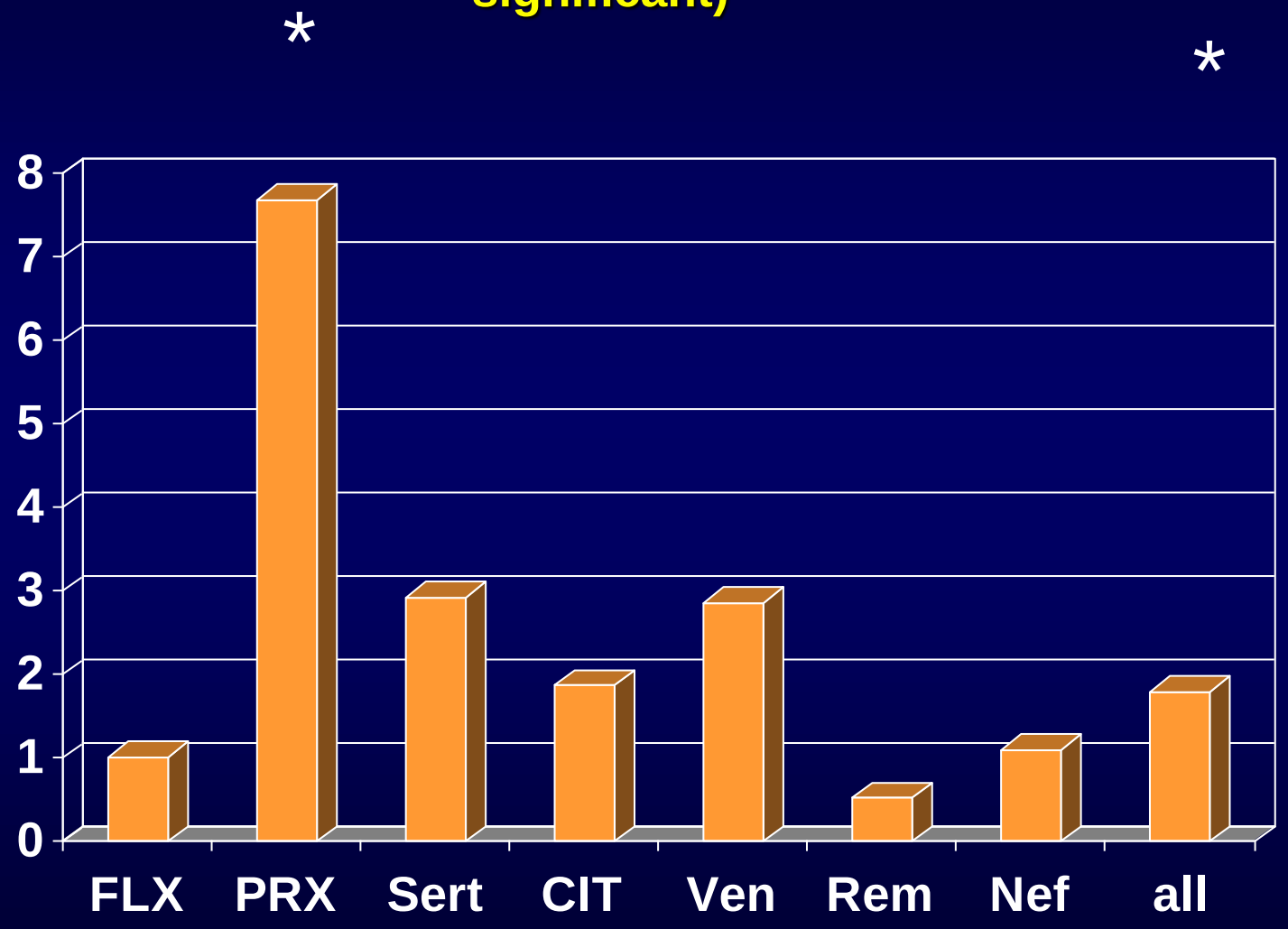
EFFECT OF ANTI-DEPRESSANTS ON OVERALL SUICIDE RATE ISN'T CLEAR



Milane et al
PLOS Medicine
3(6) e 90
June 2006
www.plosmedicine.org

Relative Risk of Activation

(note: confidence intervals very wide; * means statistically significant)



Age effects on behavioral toxicity

- Number Needed to Harm (NNH) for Mood Stabilizer use after 3 months of Antidepressant (Martin et al., 2004)
  - Ages 5-9,nnh 13;Ages 25-29 nnh 29
- Review of SSRI trials (Safer and Zito, 2006) **child** average **10.7%** (32 of 298) for active drug and 3.4% (10 of 294) for placebo; **adolescents** average **2.1%** (13 of 622) for SSRIs and 1.9% (10 of 538) for placebo.
- Rates of disinhibition in children <age 8 significantly higher than those over age 8 (Carlson and Mick, 2003)
- >350 teens have been enrolled in carefully done med trials with up to 1 year follow up. < 5 cases of mania – if that.

Bottom line re: overall adverse events

- Somatic effects not that different from placebo
- Usually <10%
- The AEs of greatest psychiatric relevance and concern are behavioral activation and suicidal behavior
  - Activation rates vary widely from 2-26%
  - Younger children are more vulnerable
  - Children with developmental disabilities are more vulnerable

Bottom line on Suicidality (so far)

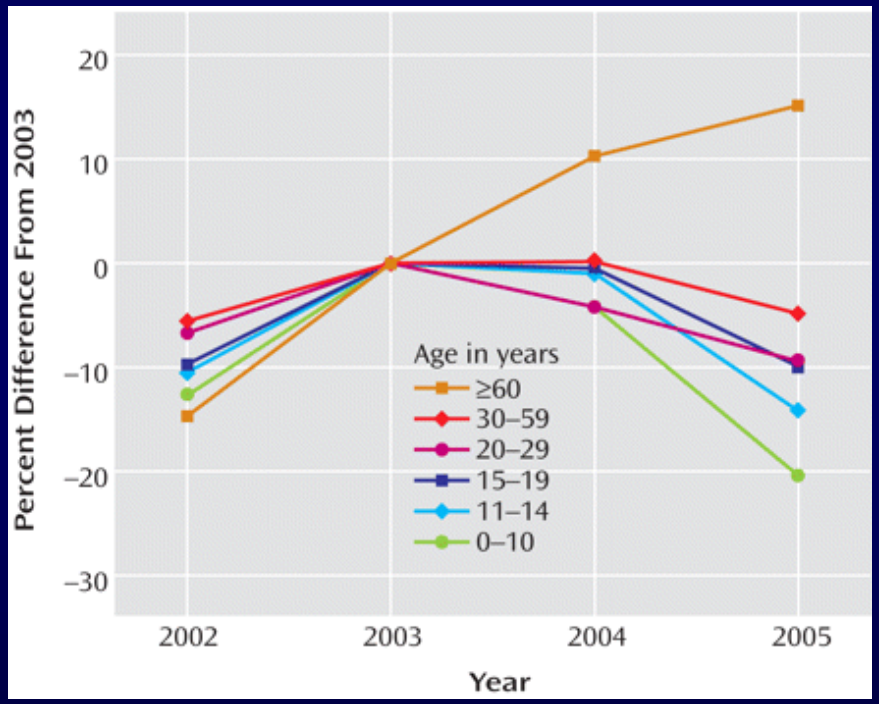
- The suicidal behavior rate (mostly ideation and threat, few attempts, no suicides) is low but always higher on medication
- “emergence” of suicidal behavior on meds is about 3-4% compared to ~1-2% in placebo treated kids
- There is a relationship between age and suicidal behavior; rates are higher in younger people-up to age 25 in fact.
- There is a relationship between disorder and suicidality; rates are higher in young people treated for depression
- The number of 6-17 year olds one needs to see to get a response is about 10; the number to see before seeing suicidal behavior is about 112.
- While primary outcomes were established a priori, measures of suicidal behavior were not

Internalizing disorders medication treatment score card (Bridge et al., JAMA, 2007)

	# studies # patients	AntiD resp Pbo Resp Prd*	NNT	SuiB AD SuiB Pbo Prd	NNH	E.S.
MDD	13 2910	61%;50% 11%	10	3%; 2% 1%	112	.25
OCD	6 705	52%;32% 20%	6	1%; 0.3% .5%	200	.48
Anxiety	6 1136	69%;39% 30%	3	1%; 0.2% 0.7%	143	.69

Prd=Pooled risk difference like Absolute Treatment Benefit

SSRI Rx Rates in USA, 2002–2005, Stratified by Age Group -Expressed as a % of the 2003 Rate



Gibbons RD et al. Am J Psychiatry. 2007; 164(9):1356-63.

Largest national database of longitudinal Integrated health care claims from 1999-2007; 1^{o} care-44% decrease for kids, 29% adults; no substitute care to offset in kids

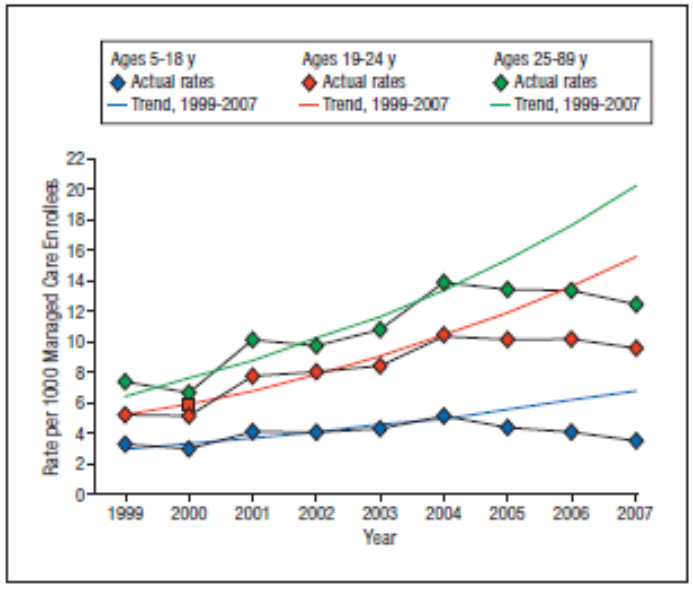
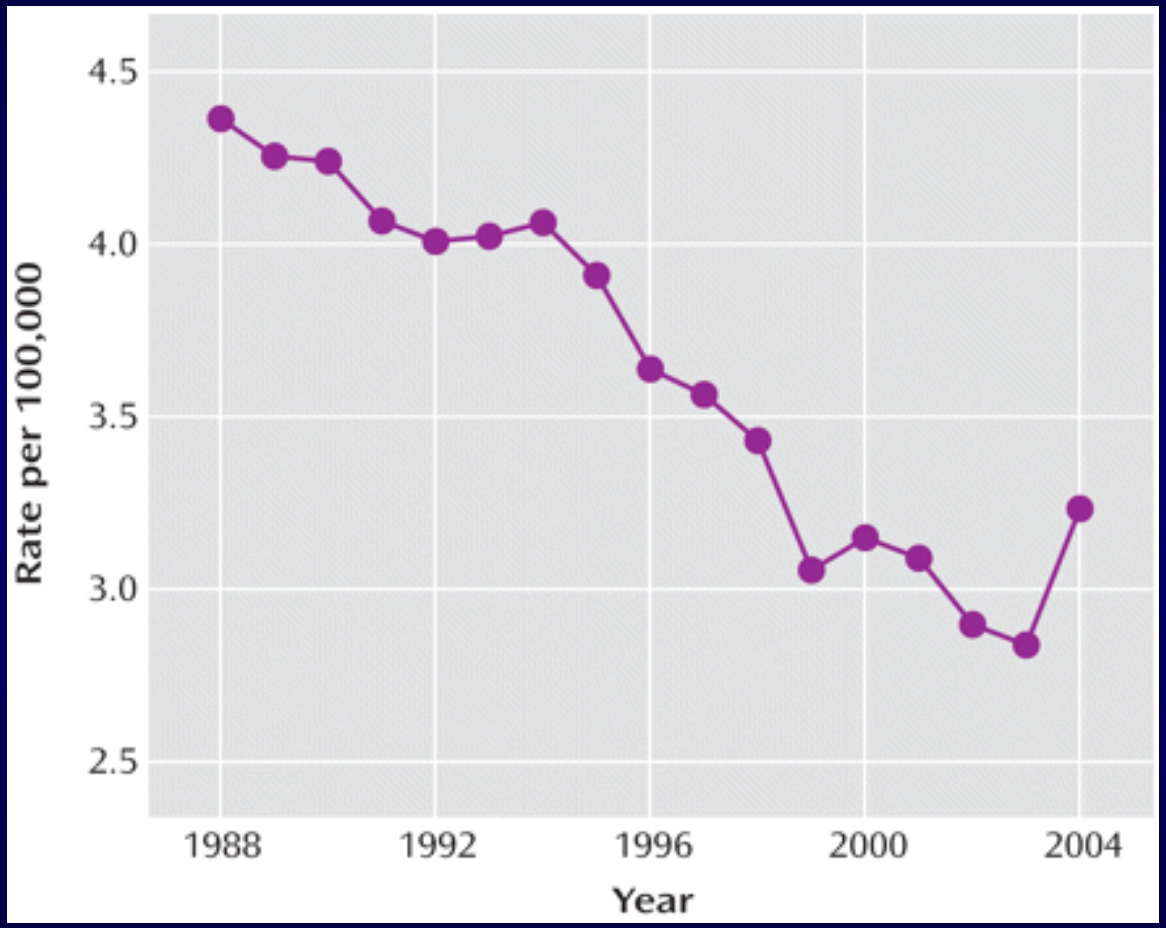


Figure 1. PHARMetrics Patient Centric Database population rates of major depressive disorder (actual and predicted) by age group (male and female individuals combined).

Libby et al., AGP 2009; 66:633-39

Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



Gibbons RD et al. Am J Psychiatry. 2007; 164(9):1356-63.

Editorial: How Can We Know Whether Antidepressants Increase Suicide Risk? Gregory E. Simon, M.D.

What to tell patients:

"The Food and Drug Administration requires a warning that antidepressant medications can sometimes cause or increase thoughts of suicide. That is because studies in children, adolescents [and young adults] have shown that antidepressants can increase suicidal thoughts.

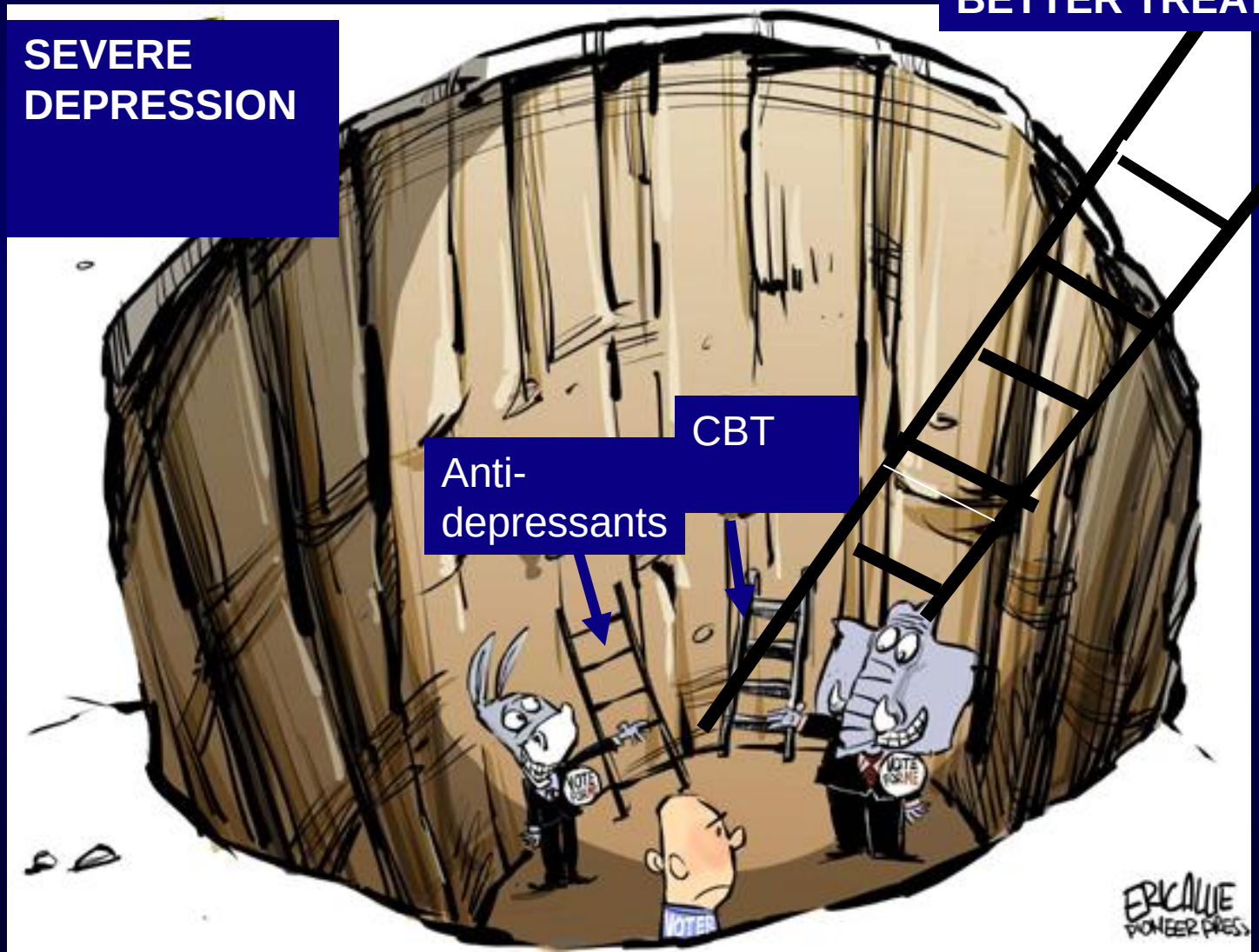
However, other studies have shown that the overall risk of attempting suicide goes down after starting antidepressant medication.

Even if antidepressants help most people who take them, some people may have very negative reactions. Thus, it is important that we have regular contact over the next few weeks. If you have thoughts about suicide or about harming yourself, please contact me right away. "

My Summary of Data for Pediatric Depression and Anxiety

- Benefit of most antidepressants in children and adolescents for depression (outside of fluoxetine) is often modest.
- Benefit in anxiety disorders is better in part because placebo responses are lower.
- Risks of suicidal behavior and activation are small but consistently associated with antidepressant medication and in younger patients
- Given the morbidity of mood and anxiety disorders in children and adolescents treatment should be vigorously pursued
- It is just necessary to be honest about both the benefits and risks

Severe depression is a deep hole; we need better ways to get out of it



For more information, please go to the main website and browse for workshops on this topic or check out our additional resources.

Additional Resources

Online resources:

1. Society of Clinical Child and Adolescent Psychology website: http://effective childtherapy.com
2. National Alliance on Mental Illness website: http://www.nami.org/

Selected Peer-reviewed Journal Articles:

1. Bridge J., Iyengar S., Salary C., Barbe, R.P., Birmhaer, B., Pincus, H.A. et al. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association, 297,* 1683-1696.
2. Emslie G., Heiligenstein J., Hoog S., Wagner, K.D., Findling, R.L., McCracken, J.T., et al. (2004). Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*, 1397-1405.
3. Goodyer I., Dubicka B., Wilkinson P., Kelvin R., Roberts C., Byford S., et al (2007). Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behavior therapy in adolescents with major depression: randomized controlled trial. *British Medical Journal*, *335*, 142-149.
4. TADS Team (2009). The treatment for adolescents with depression study (TADS): Outcomes over 1 year of naturalistic follow-up. *American Journal of Psychiatry*, *166*, 1141-1149
5. Vitiello B., Emslie G., Clarke G., Wagner KD., Asarnow JR., Keller MB., et al (2011) Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *Journal of Clinical Psychiatry*, *72(3*), 388-96.
6. Wagner K.D., Ambrosini, P., Rynn, M., Wohlberg, C., Yang, R., Greenbaum, M.S., et al. (2003). Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: Two randomized controlled trials. *The Journal of the American Medical Association, 290 (8),* 1033-1041.
7. Walkup, J.T. (2010). Treatment of depressed adolescents. *American Journal of Psychiatry, 167*, 734-737.

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