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Black-Box Warnings: Benefits & Risks: the Case of Antidepressants & "Suicidality"

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Disclosures
–2008–

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Is a consultant to, or has collaborated in research with: Alkermes, Auritec, Biotrofix, IFI, Janssen, JDS, Lilly, Merck, NeuroHealing, Novartis, and Solvay Corporations

But has no speakers' panel or equity relationships with industrial organizations

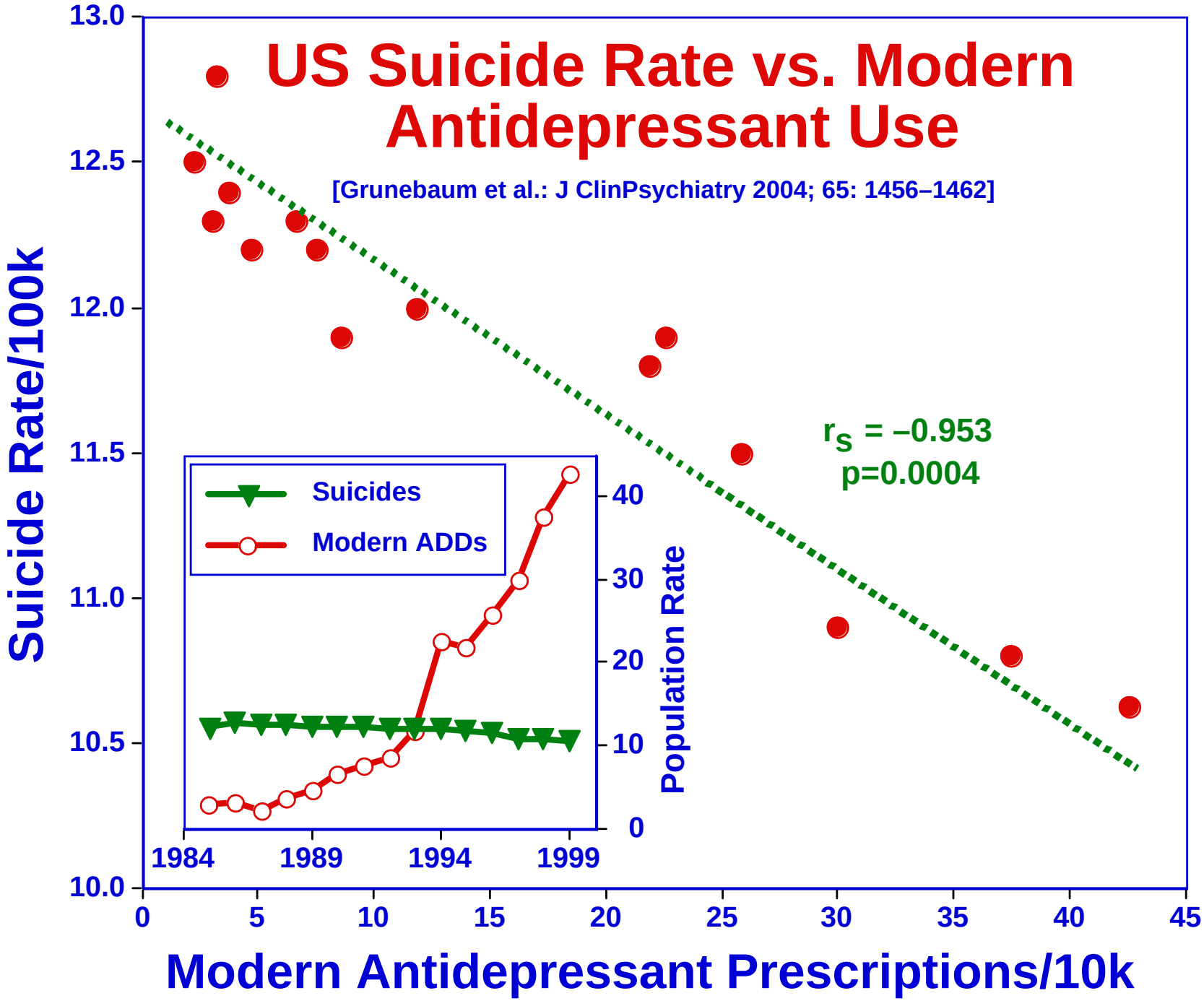
…If one were to give an anxious, agitated depressive a drug with a disinhibiting, activating effect…then one would have to be aware of the likelihood of increasing the risk of suicide. It would be preferable in such patients to begin with a more sedative treatment…

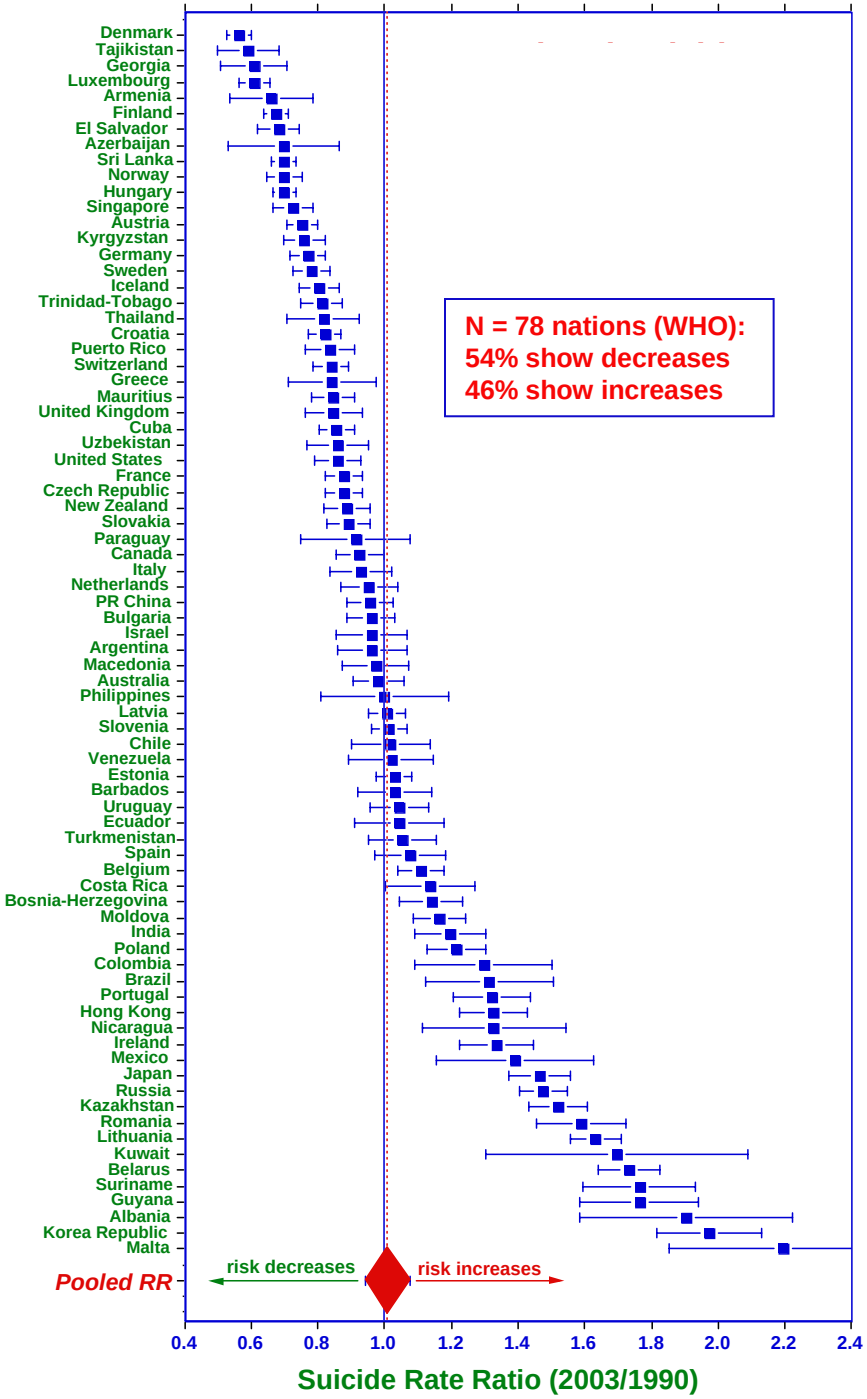
Paul Kielholz & Walter Pöldinger 1969

Growing concern about possible associations of drug treatments with "suicidal" risks

- Antidepressants: early suspicions (Kielholz & Pöldinger 1960s, Teicher et al. 1990s, Healy 1990s)
- Antidepressants in juveniles and young adults, based on post-hoc, age-stratified analyses of RCT data (2003–2006)
- Appetite-suppressant cannabinoid receptor antagonist: *rimonabant* [Accomplia®, Zimulti®, Sanofi-Aventis] (2007)
- Anti-smoking nicotinic partial-agonist: *varenicline* [Chantix®, Pfizer) (2007)
- All anticonvulsants (2008)
- FDA considers broad application of Columbia suicidal rating scale vs. current *passive and incidental* reporting of suicidal risks (2008)

TIME – November 21, 2005


US Suicide Rate vs. Modern Antidepressant Use
[Grunebaum et al.: J ClinPsychiatry 2004; 65: 1456–1462]
r_s = –0.953
p=0.0004
Suicide Rate/100k
Modern Antidepressant Prescriptions/10k
Suicides
Modern ADDs
Population Rate
13.0
12.5
12.0
11.5
11.0
10.5
10.0
0
5
10
15
20
25
30
35
40
45
1984
1989
1994
1999



N = 78 nations (WHO):
54% show decreases
46% show increases

International Suicide Rates: 2003 vs. 1990

[Baldessarini et al.: *Harvard Rev Psychiatry* 2007]

Factors associate d with US state suicide r ates (2001)

Factors	Corr. (r)	*p*
Population density	–0.735	<0.001
Male sex	+0.576	<0.001
Annual income/capita	–0.550	<0.001
Psychiatrists/100,000	–0.544	<0.001
Native-American (%)	+0.543	<0.001
Physicians/100,000	–0.528	<0.001
Federal MH aid	–0.443	0.001
African-American (%)	–0.430	0.002
Uninsured residents (%)	+0.391	0.005

From Tondo et al.: J Clin Psychiatry 2006; 67: 517–523 (for 50 states+DC).

Meta-analyses: Suicidal acts in antidepressant trials

Comparison	Trials	RR	[95%CI]	*p*
All agents vs. controls	20	1.06	[0.74–1.52]	0.77
Very large studies omitted	16	1.03	[0.60–1.76]	0.91

RR = Risk-Ratio with confidence-interval (rates of suicides or attempts with placebo or other control vs. with antidepressant treatment).

Of note, rates of suicidal acts in RCTs are at least as large as in clinical samples of MDD patients, reflecting acute illness + ineffective screening.

[From Baldessarini et al. 2007]

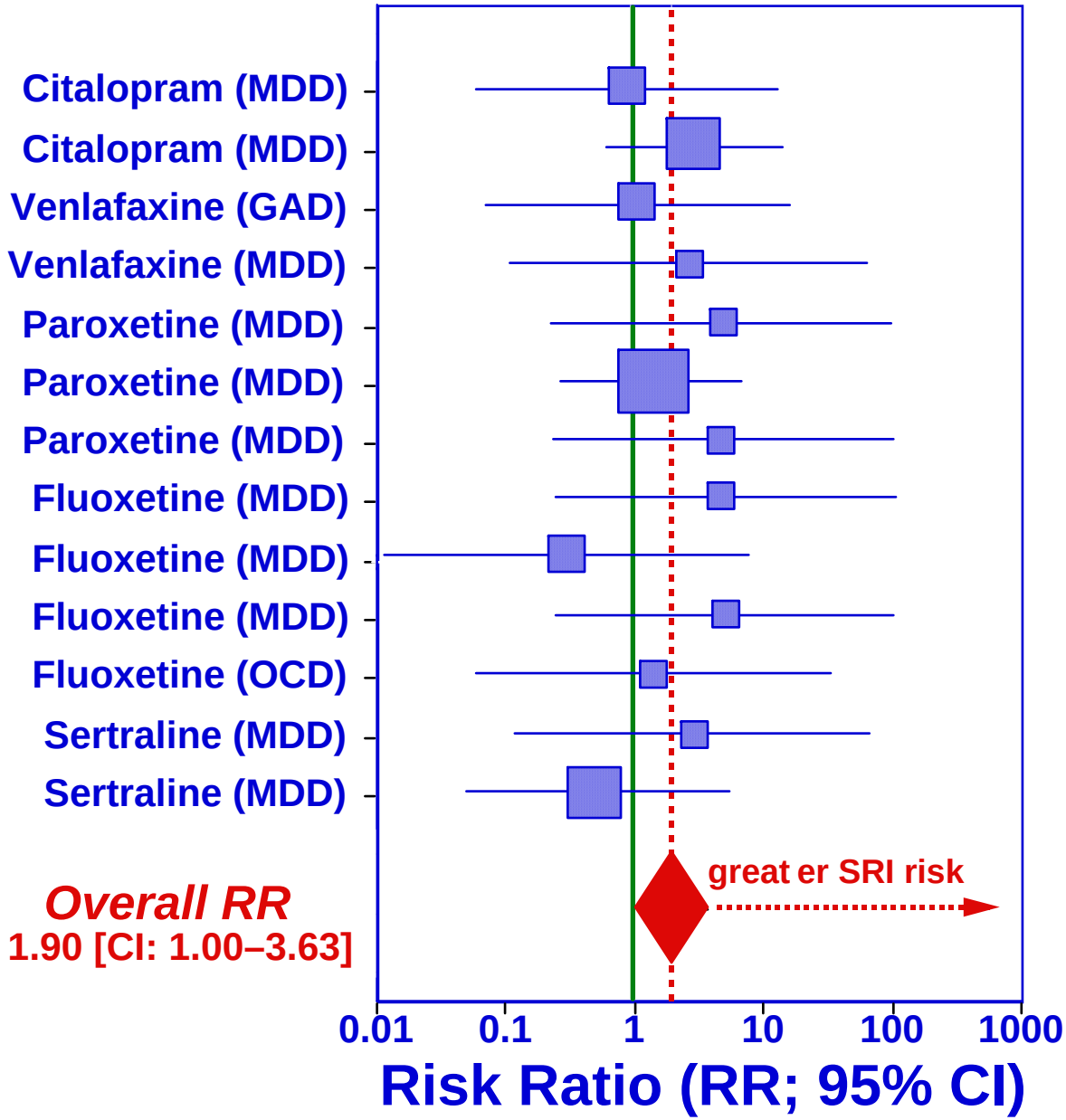
Pooled meta -analyses of Antidepressa nt RCTs

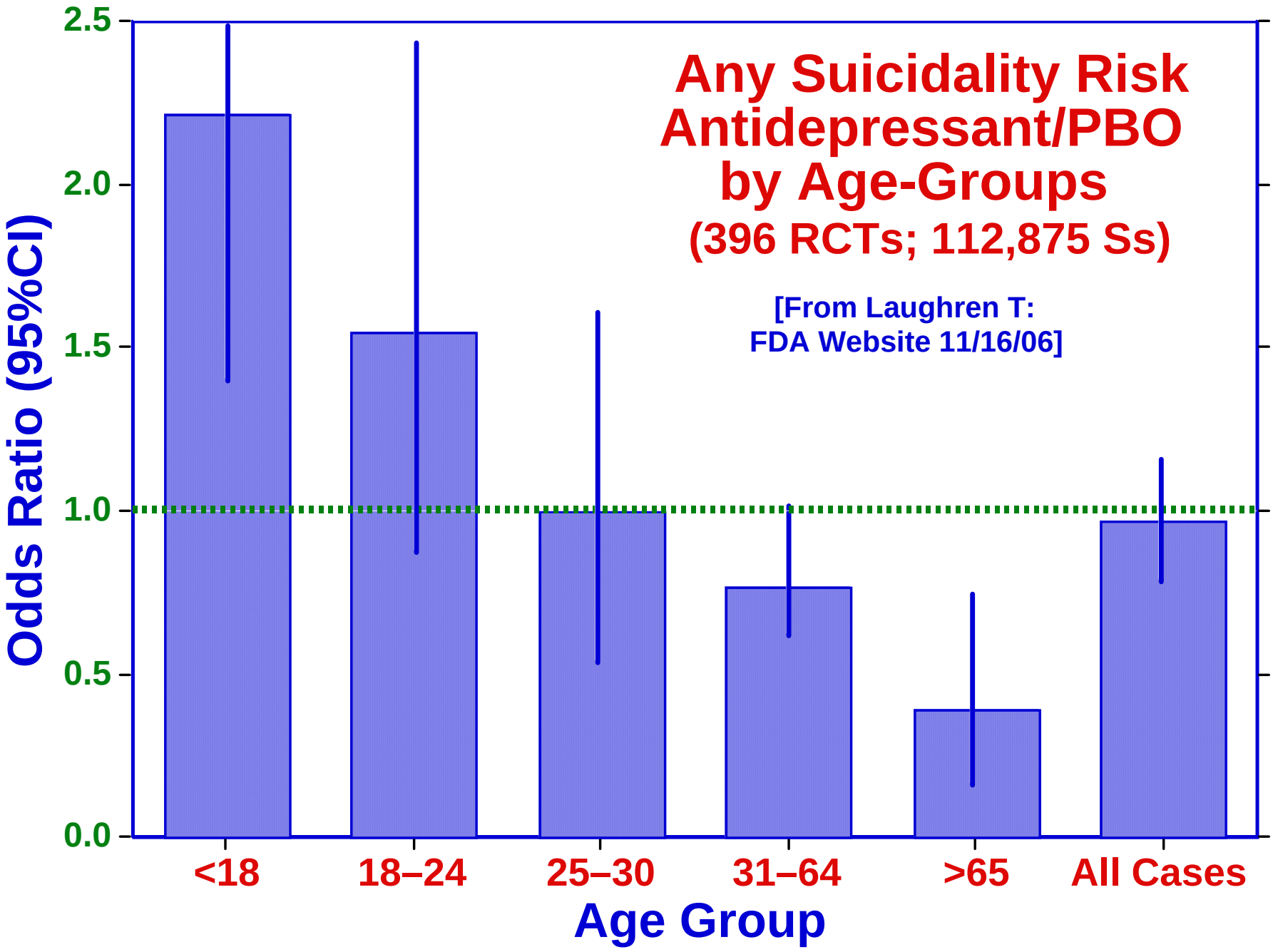
Outcomes	NNH	[95% CI]	*z*	*p*
Suicides	4651	[1675–]	1.11	0.27
Attem pts	613	[321–6993]	2.15	0.03
All Acts	667	[373–3135]	2.49	0.01

Based on ran do m-effects, RD m eta-analys es of data c ompile d by Khan et al. 2000, 2003; Fergusson et al. 2005; Gunnel l et al. 2005; Acha rya et al. 2006; Lau ghren 2006, involving some 160,400 subje cts in over 200 rand omiz ed, place bo-controlled trials in adults wi th maj or depr ession (Fro m Bald essarini & Tondo, 2007).

Suicide Attempts: Juvenile SRI Trials

[From Hammad TA: FDA, 2004]

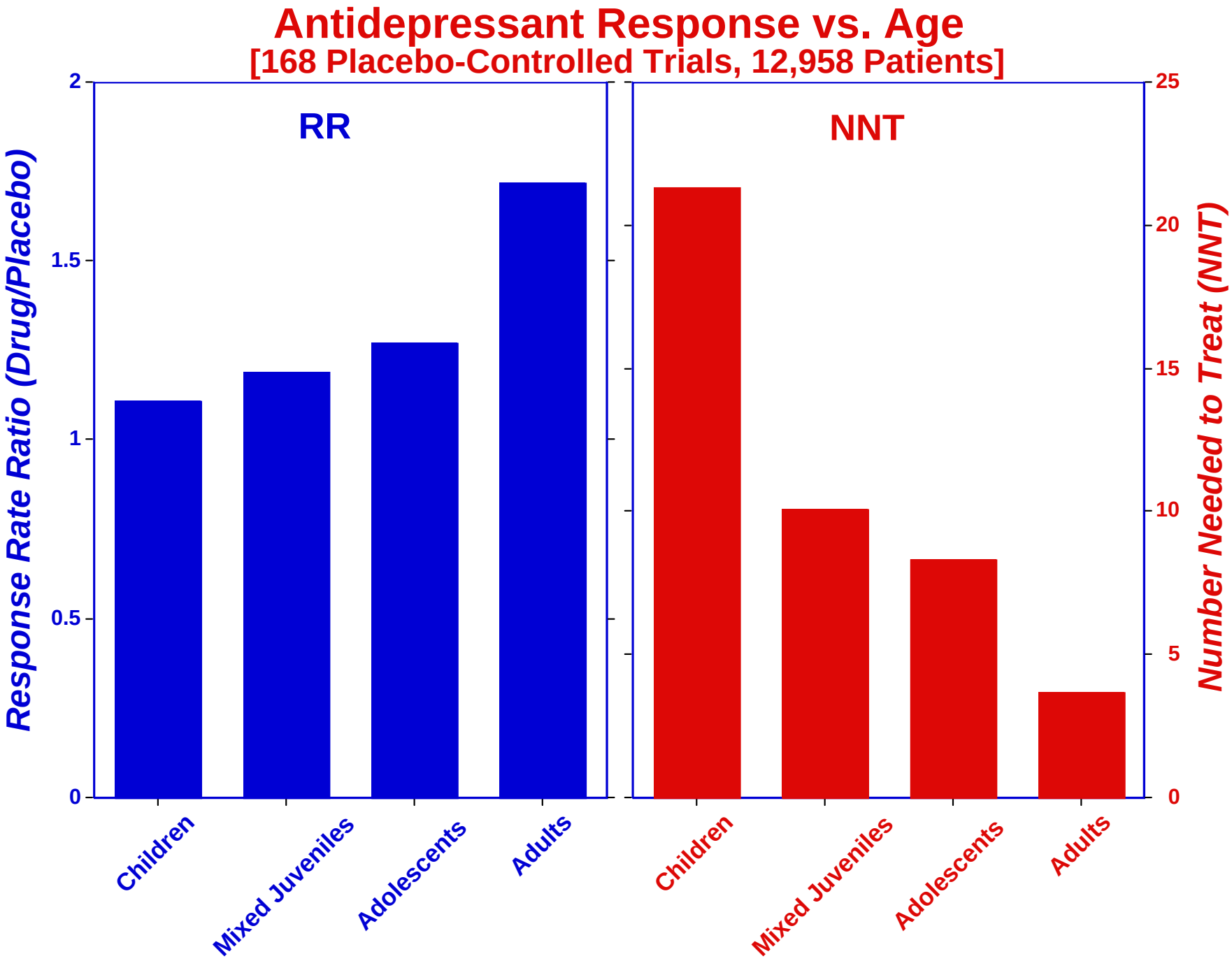



Any Suicidality Risk
Antidepressant/PBO
by Age-Groups
(396 RCTs; 112,875 Ss)
[From Laughren T:
FDA Website 11/16/06]
Odds Ratio (95%CI)
2.5
2.0
1.5
1.0
0.5
0.0
<18
18–24
25–30
31–64
>65
All Cases
Age Group

Meta-analytic comparisons: Response rate-ratios (RR) from antidepressant RCTs for juvenile depression

Subgroups	Trials	RR	[95%CI]	*p*
All agents	30	1.22	[1.15–1.31]	<0.0001
TCAs	14	1.15	[0.98–1.34]	0.092
SRIs	12	1.23	[1.14–1.33]	<0.0001
Other agents	4	1.27	[1.06–1.52]	0.008

From Tsapakis et al. Br J Psychiatry 2008.
Also see ISCTM poster, 2/26/08.

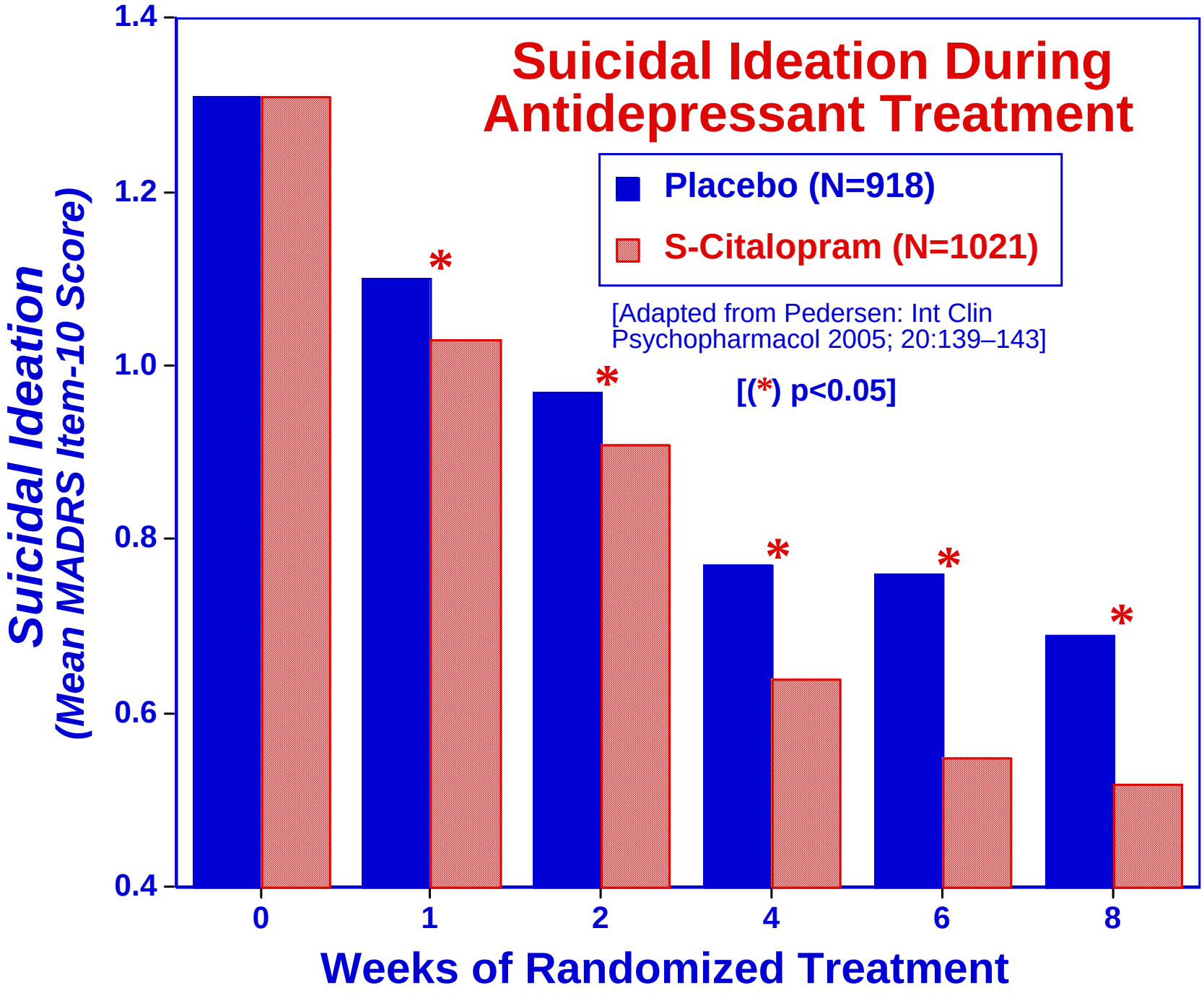

Antidepressant Response vs. Age
[168 Placebo-Controlled Trials, 12,958 Patients]
RR
NNT
Response Rate Ratio (Drug/Placebo)
Number Needed to Treat (NNT)
2
1.5
1
0.5
0
25
20
15
10
5
0
Children
Mixed Juveniles
Adolescents
Adults
Children
Mixed Juveniles
Adolescents
Adults

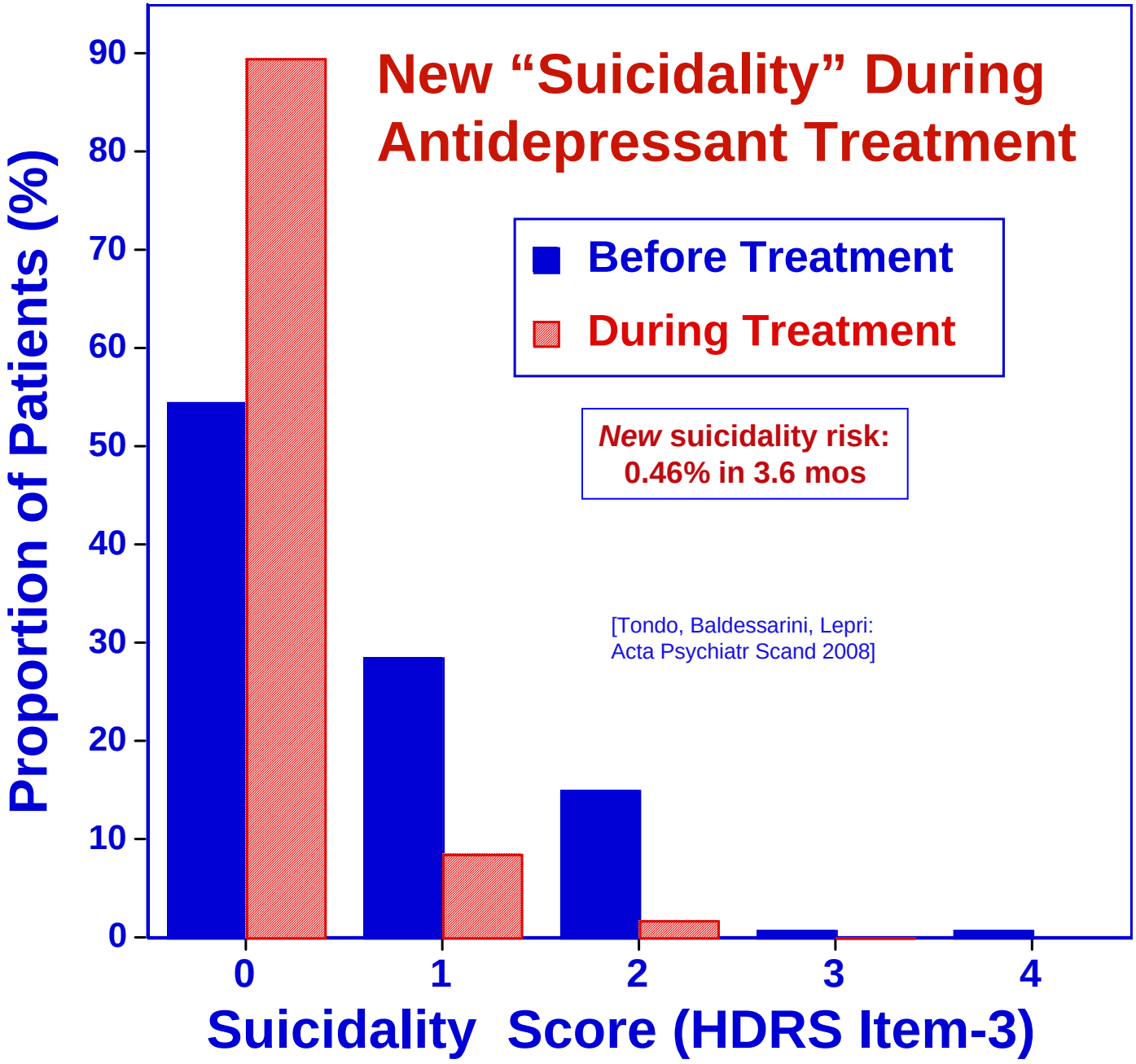
Suicidal ideation vs. behavior: Relative risks

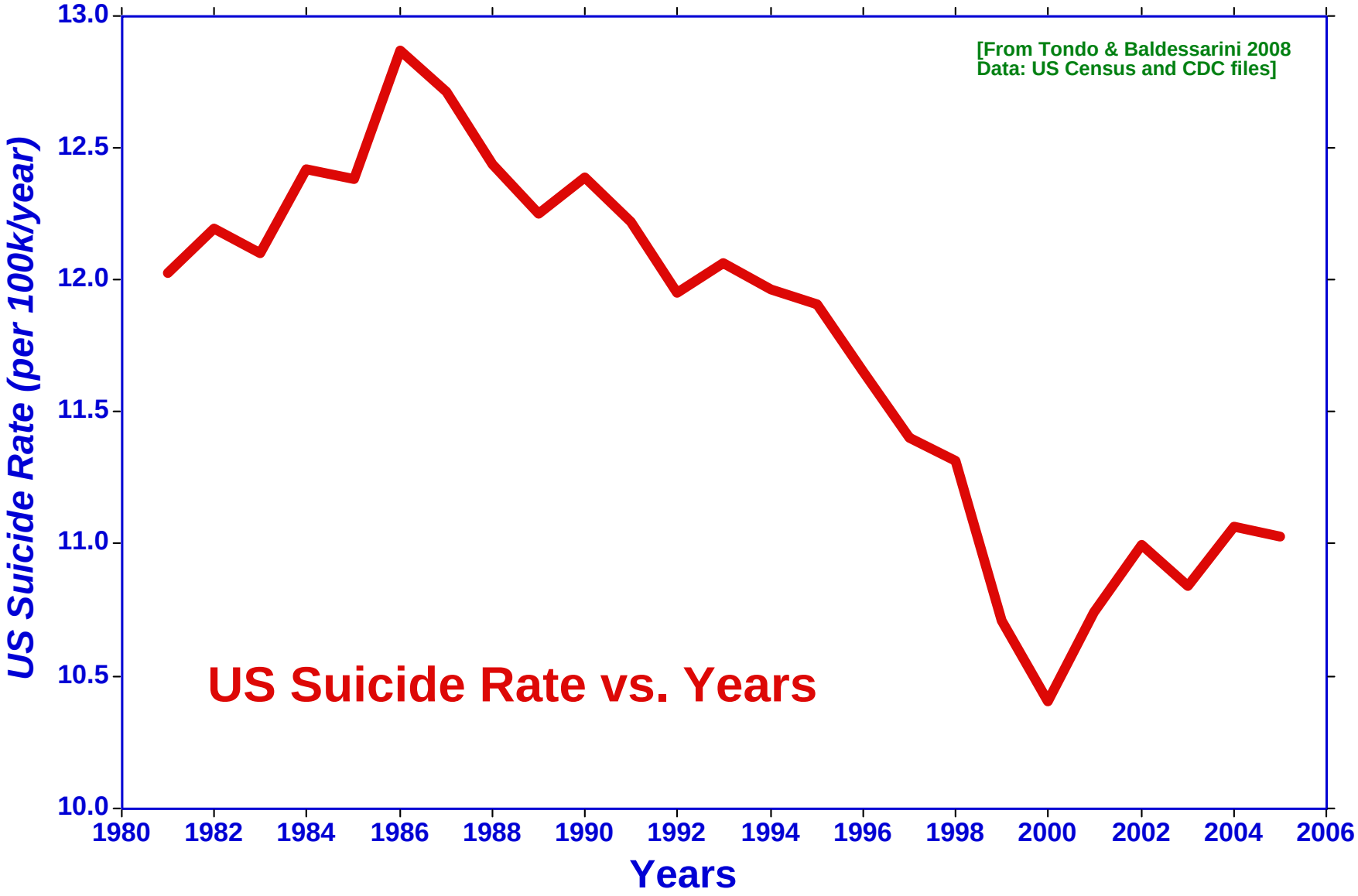
Comparisons	Genl Pop	Mood Dxs
[I+A]/S	4.4/0.011 = 400	16.7/0.21 = 80
I/S	3.9/0.011 = 355	15.2/0.21 = 72
A/S	0.5/0.011 = 45	1.6/0.21 = 8

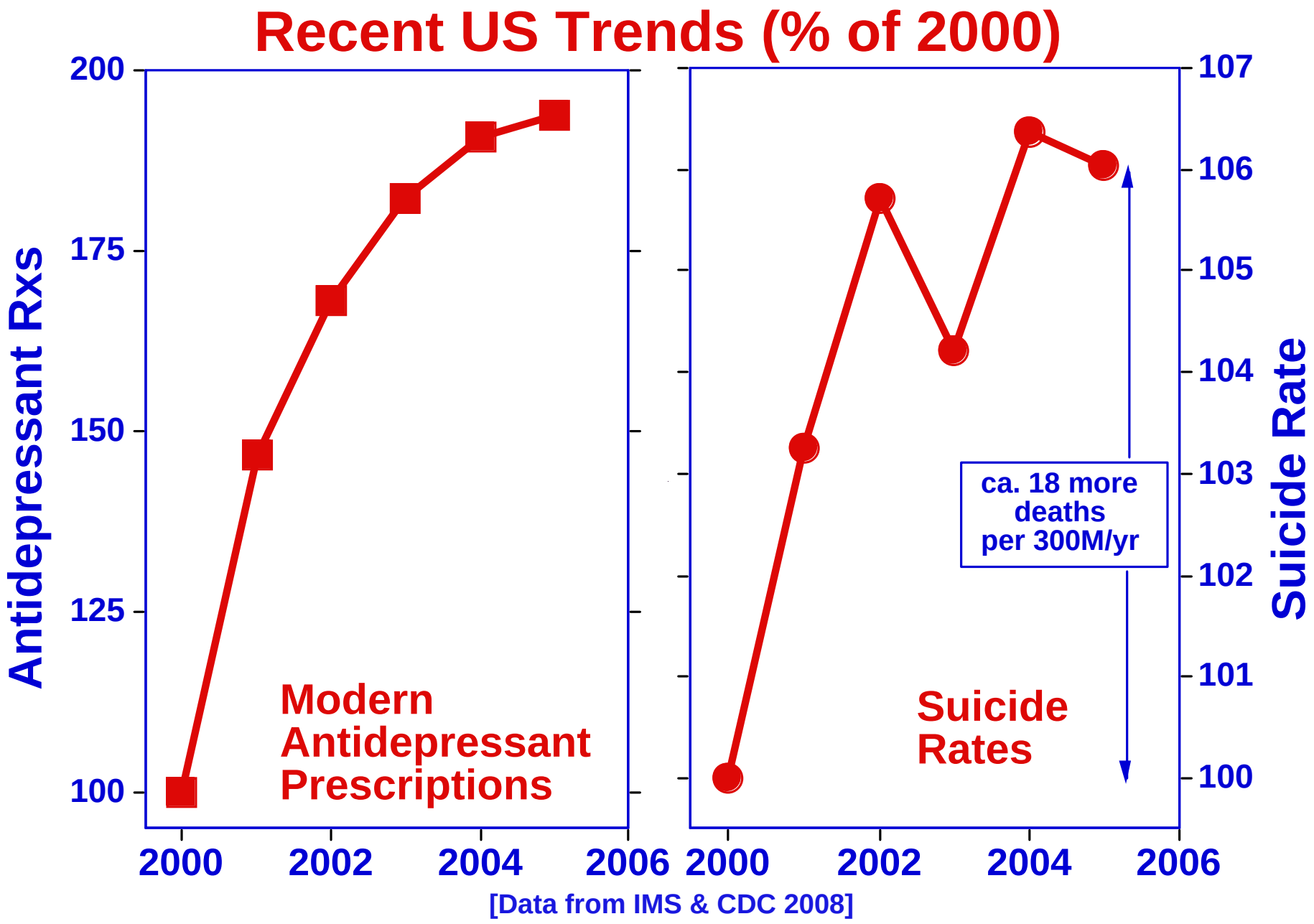
A = *Attempts*, I = *Ideation*, S = *Suicides*.

Adapted from Kessler et al. JAMA 2005; 293: 2487–1395;
Tondo et al. Acta Psychiatr Scand 2007; 116: 419–428.


Suicidal Ideation During Antidepressant Treatment
Placebo (N=918)
S-Citalopram (N=1021)
[Adapted from Pedersen: Int Clin Psychopharmacol 2005; 20:139–143]
[(*) p<0.05]
Suicidal Ideation
(Mean MADRS Item-10 Score)
1.4
1.2
1.0
0.8
0.6
0.4
*
*
*
*
*
0
1
2
4
6
8
Weeks of Randomized Treatment


New “Suicidality” During Antidepressant Treatment
Before Treatment
During Treatment
New suicidality risk: 0.46% in 3.6 mos
[Tondo, Baldessarini, Lepri: Acta Psychiatr Scand 2008]
Proportion of Patients (%)
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
Suicidality Score (HDRS Item-3)

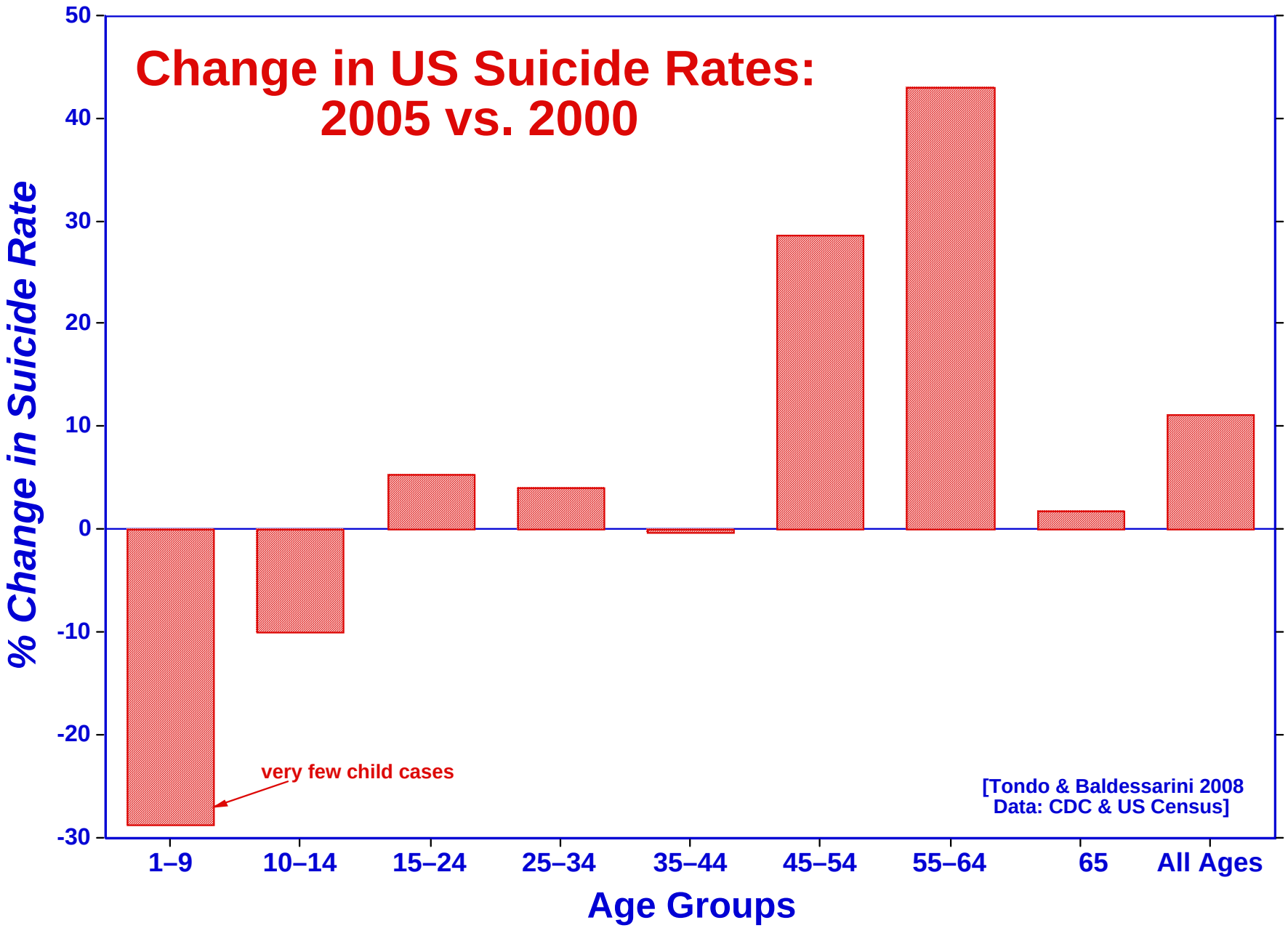

[From Tondo & Baldessarini 2008
Data: US Census and CDC files]
US Suicide Rate vs. Years
US Suicide Rate (per 100k/year)
13.0
12.5
12.0
11.5
11.0
10.5
10.0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
Years


Recent US Trends (% of 2000)
Antidepressant Rxs
200
175
150
125
100
Modern
Antidepressant
Prescriptions
2000
2002
2004
2006
Suicide Rate
107
106
105
104
103
102
101
100
ca. 18 more
deaths
per 300M/yr
Suicide
Rates
2000
2002
2004
2006
[Data from IMS & CDC 2008]

US antide pressant prescription rates & new diagnos es of MDD : 2005 vs. 2003

Study	Juveniles	Adults
Antidepressant Rxs		
Nemeroff et al. 2007	–20.8%	–4.5%
Libby et al. 2007	–55.6%	——
Valuck et al. 2007	——	–59.5%
Gibbons et al. 2007	–17.0%	–9.0%
Averages	–31.3%	–18.3%
New MDD diagnoses		
Libby et al. 2007	–17.0%	——
Valuck et al. 2007	——	+9.0%

All reports are in Am J Psychiatry 2007. Nemeroff considered all anti-Depressants; others only SSRIs. The findings have been interpreted as a selective adverse impact of FDA safety warnings on juvenile care.


Change in US Suicide Rates:
2005 vs. 2000
% Change in Suicide Rate
50
40
30
20
10
0
-10
-20
-30
very few child cases
[Tondo & Baldessarini 2008
Data: CDC & US Census]
1–9
10–14
15–24
25–34
35–44
45–54
55–64
65
All Ages
Age Groups

FDA clinical guidelines for antidepressant therapy

- Monitor depressed patients closely *early*
- Intervene if depression or suicidality worsen
- Beware of emerging "activation"
  (*anger, restlessness, insomnia, mania*)
- Discontinue antidepressants *slowly*
- Screen for occult bipolar disorder
- Educate patient and family about risks

FDA, March 2004: Intended for adults & children.

Clinical follow-up of US patients newly prescribed antidepressants

Weeks	*Visits/person*[a] Any	MH	FDA
0–4	1.65	0.40	4.00
0–8	3.11	0.75	6.00
0–12	4.48	1.05	7.00

Years	*Meet FDA Guidelines*[b] Any	MH
1998–2003	10.8%	7.0%
2003–2005	13.4%	10.3%

FDA guidelines (2003): face-to-face return visits at weeks 1, 2, 3, 4, 6, 8 & 12 (7 visits/3 months)

MH = psychiatrist or other mental-health specialist. Any = any clinician. Results for juveniles & adults were very similar.

a. Stettin et al. Am J Manag Care 2006; 12: 453–461 (re. 2001–2003).

b. Morrato et al. Am J Psychiatry 2008; 165: 42–50 (re. 1998–2005).

Conclusions: Benefits & risks associated with black-box warnings re. "suicidality"

Potential Benefits

- Greater awareness of potential risks of treatments
- Improved patient assessment & closer follow-up
- Reduced liability risks to manufacturers
- Improved methods to assess specific safety risks
- Greater awareness of treatment-effects on suicide

Possible Risks

- Increased liability of clinicians to malpractice claims
- Clinical reluctance to diagnose and treat: suicide ↑ ??
- Adverse impact on pharmaceutical markets
- Adverse impact on FDA if questionable policies rest on weak science
- Increased costs of care: ↑ drug prices, ↑ litigation